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<p>(54) Title: FUSED RING ANALOGS OF NITROGEN CONTAINING NONAROMATIC HETEROCYCLES</p> <div style="text-align: center;"> <p>(I)</p> </div> <p>(57) Abstract</p> <p>The present invention relates to novel fused ring analogs of nitrogen containing heterocycles, and specifically, to compounds of formula (I), wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, x, y, and z and m are defined as below. These novel compounds are useful in the treatment of inflammatory and central nervous system disorders, as well as other disorders.</p>		

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FUSED RING ANALOGS OF NITROGEN
CONTAINING NONAROMATIC HETEROCYCLES

Background of the Invention

The present invention relates to novel fused ring
analogs of nitrogen containing heterocycles, pharmaceutical
10 compositions comprising such compounds and the use of such
compounds in the treatment and prevention of diseases
mediated by or resulting, directly or indirectly, from an
excess of substance P. The invention also relates to novel
intermediates used in the synthesis of such compounds.

15 Substance P is a naturally occurring undecapeptide
belonging to the tachykinin family of peptides, the latter
being named because of their prompt stimulatory action on
smooth muscle tissue. More specifically, substance P is a
pharmacologically-active neuropeptide that is produced in
20 mammals (having originally been isolated from gut) and
possesses a characteristic amino acid sequence that is
illustrated by D.F. Veber et al. in U.S. Patent No.
4,680,283. The wide involvement of substance P and other
tachykinins in the pathophysiology of numerous diseases has
25 been amply demonstrated in the art. For instance,
substance P has recently been shown to be involved in the
transmission of pain or migraine [see B.E.B. Sandberg et
al., Journal of Medicinal Chemistry, Vol. 25, p. 1009
(1982)], as well as in central nervous system disorders
30 such as anxiety and schizophrenia, in respiratory and
inflammatory diseases such as asthma and rheumatoid
arthritis, respectively, in rheumatic diseases such as
fibrositis, and in gastrointestinal disorders and diseases
of the GI tract such as ulcerative colitis and Crohn's
35 disease, etc. (see D. Regoli in "Trends in Cluster
Headache," edited by F. Sicuteri et al., Elsevier
Scientific Publishers, Amsterdam, 1987, pp. 85-95).

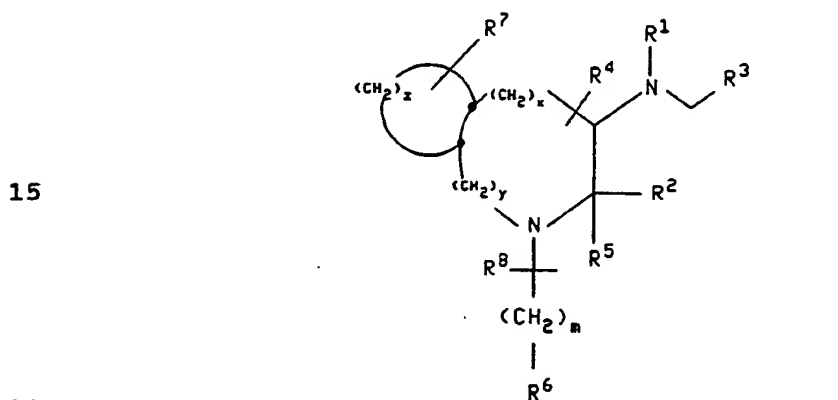
PCT Patent Application PCT/US 90/00116, filed January
4, 1990, refers to carbocyclic ring systems wherein one
40 of the rings is substituted with an amino group and wherein
one carbon atom in each of two of the rings may be replaced

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by a hetero atom, and states that they are useful as substance P antagonists. PCT Patent Application PCT/US 89/05338, filed November 20, 1989 and U.S. Patent Applications 07/557,442 and 07/532,525, filed July 23, 1990 and June 1, 1990, respectively, refer to amino substituted quinuclidine derivatives and state that they are useful as substance P antagonists.

Summary of the Invention

The present invention relates to compounds of the
10 formula



wherein x is an integer from zero to four;

y is an integer from zero to four;

z is an integer from one to six;

the ring containing $(CH_2)_z$ may contain from zero to
25 three double bonds, and one of the carbons of $(CH_2)_z$ may optionally be replaced by oxygen, sulfur or nitrogen;

m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double or triple bond, and any
30 one of the carbon atoms of $(CH_2)_m$ may optionally be substituted with R^8 (as indicated by the horizontal line adjacent to R^8 in structure I);

R^1 is hydrogen or (C_1-C_8) alkyl optionally substituted with hydroxy, alkoxy or fluoro;

35 R^2 is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen,

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oxygen or sulfur; aryl selected from phenyl and naphthyl;
heteroaryl selected from indanyl, thienyl, furyl, pyridyl,
thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl,
tetrazolyl, and quinolyl; phenyl (C₂-C₆) alkyl, benzhydryl
5 and benzyl, wherein each of said aryl and heteroaryl groups
and the phenyl moieties of said benzyl, phenyl (C₂-C₆) alkyl
and benzhydryl groups may optionally be substituted with
one or more substituents independently selected from halo,
nitro, (C₁-C₆) alkylamino, (C₁-C₆) alkoxy, trifluoromethyl,
10 amino,

O O

(C₁-C₆)-alkylamino, (C₁-C₆)alkyl-O-C-, (C₁-C₆)alkyl-O-C-(C₁-
15 O O
C₆)alkyl, (C₁-C₆)alkyl-C-O-, (C₁-C₆)alkyl-C-(C₁-C₆)alkyl-O-,
O O
20 (C₁-C₆)alkyl-C-, (C₁-C₆)alkyl-C-(C₁-C₆)alkyl-, di-(C₁-C₆)
O O
25 alkylamino, -CNH-(C₁-C₆)alkyl, (C₁-C₆)alkyl-C-NH-(C₁-C₆)alkyl,
O O
-NHCH and -NHC-(C₁-C₆)alkyl;

30 R⁵ is hydrogen or (C₁-C₆)alkyl;
or R² and R⁵, together with the carbon to which they
are attached, form a saturated carbocyclic ring having from
3 to 7 carbon atoms, wherein one of said carbon atoms may
35 optionally be replaced by oxygen, nitrogen or sulfur;
R³ is aryl selected from phenyl and naphthyl;
heteroaryl selected from indanyl, thienyl, furyl, pyridyl,
thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl,
tetrazolyl, and quinolyl; or cycloalkyl having from three
40 to seven carbon atoms, wherein one of said carbon atoms may
optionally be replaced by nitrogen, oxygen or sulfur;
wherein each of said aryl and heteroaryl groups may
optionally be substituted with one or more substituents,
and said (C₃-C₇) cycloalkyl may optionally be substituted

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with one or two substituents, said substituents being independently selected from halo, nitro, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, trifluoromethyl, phenyl, amino, (C₁-C₆)-

5 alkylamino, $\begin{array}{c} \text{O} \\ || \\ -\text{CNH}-(\text{C}_1-\text{C}_6)\text{alkyl} \end{array}$, $\begin{array}{c} \text{O} \\ || \\ (\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}-\text{NH}-(\text{C}_1-\text{C}_6)\text{alkyl} \end{array}$,
 10 $\begin{array}{c} \text{O} \\ || \\ -\text{NHCH} \end{array}$ and $\begin{array}{c} \text{O} \\ || \\ -\text{NHC}-(\text{C}_1-\text{C}_6)\text{alkyl} \end{array}$;

R⁴ may be attached to any atom of the nitrogen containing ring having an available bonding site and R⁷ may be attached to any atom of the (CH₂)₂ containing ring having
 15 an available bonding site;

R⁴, R⁶, R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxy(C₁-C₆)alkyl, (C₁-C₆)alkylamino, di-(C₁-C₆)alkylamino,

20 (C₁-C₆)alkoxy, $\begin{array}{c} \text{O} \\ || \\ (\text{C}_1-\text{C}_6)\text{alkyl}-\text{O}-\text{C}- \end{array}$,

25 $\begin{array}{c} \text{O} \\ || \\ (\text{C}_1-\text{C}_6)\text{alkyl}-\text{O}-\text{C}-(\text{C}_1-\text{C}_6)\text{alkyl} \end{array}$, $\begin{array}{c} \text{O} \\ || \\ (\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}-\text{O}- \end{array}$, (C₁-C₆)alkyl-

30 $\begin{array}{c} \text{O} \\ || \\ \text{C}-(\text{C}_1-\text{C}_6)\text{alkyl}-\text{O}- \end{array}$, $\begin{array}{c} \text{O} \\ || \\ (\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}- \end{array}$, $\begin{array}{c} \text{O} \\ || \\ (\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}-(\text{C}_1-\text{C}_6)\text{alkyl} \end{array}$, and the radicals set forth in the definition of R², with the proviso that (a) when m is 0, R⁸ is absent, (b) neither R⁴, R⁶, R⁷ nor R⁸ can form, together with the carbon to which it is attached, a ring with R⁵, and (c) R⁴ and R⁷
 35 cannot be attached to the same carbon atom.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts
 40 of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate,

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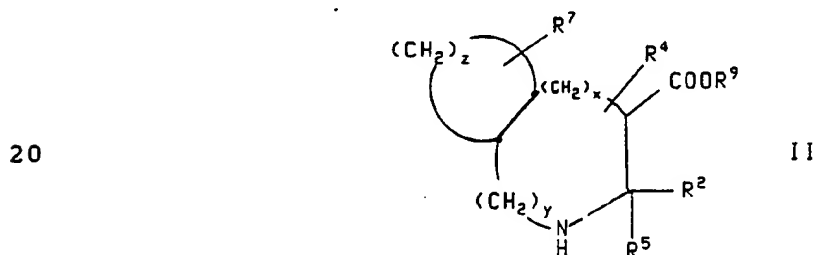
lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e.,
 5 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

The term "halo", as used herein, unless otherwise indicated, includes chloro, fluoro, bromo and iodo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon
 10 radicals having straight, branched or cyclic moieties or combinations thereof.

The term "one or more substituents," as used herein, includes from one to the maximum number of substituents possible based on the number of available bonding sites.

15 The present invention also relates to compounds of the formula



wherein R^2 , R^4 , R^5 , R^7 , x , y and z are defined as for
 25 compounds of the formula I, and R^9 is hydrogen or (C_1-C_6) alkyl. These compounds are useful as intermediates in the synthesis of compounds of the formula I.

The compounds of the formulae I and II have chiral centers and therefore exist in different enantiomeric
 30 forms. This invention relates to all optical isomers and all stereoisomers of compounds of the formula I, and mixtures thereof.

Formulae I and II above include compounds identical to those depicted but for the fact that one or more hydrogen
 35 or carbon atoms are replaced by radioactive isotopes thereof. Such radiolabelled compounds are useful as research and diagnostic tools in metabolism pharmokinetic

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studies and in binding assays. Specific applications in research include radioligand binding assays, autoradiography studies and in vivo binding studies, while specific applications in the diagnostic area include studies of the substance P receptor in the human brain in in vivo binding in the relevant tissues for inflammation, e.g. immune-type cells or cells that are directly involved in inflammatory bowel disorders and the like. Included among the radiolabelled forms of compounds of the formulae I and II are the tritium and C¹⁴ isotopes thereof.

Preferred compounds of the formula I are those wherein R¹, R⁴, R⁵, R⁶, R⁷ and R⁸ are hydrogen; R² is phenyl optionally substituted with one or more substituents independently selected from hydrogen, chlorine, fluorine, (C₁-C₆)alkoxy, (C₁-C₆)alkyl and trifluoromethyl; R³ is methoxyphenyl wherein the phenyl moiety is optionally substituted with one or more substituents independently selected from hydrogen, chlorine, fluorine, (C₁-C₆)alkoxy, (C₁-C₆) alkyl or trifluoromethyl; m is zero; and each of x, y and z is an integer from zero to four.

Specific preferred compounds of the formula I are:

[1 α ,3 α ,4 β ,5 α]-4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane;

[1 α ,3 α ,4 β ,5 α]-4-(2-chlorobenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane;

[1 α ,3 α ,4 α ,5 α]-4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane;

4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo[4.4.0]decane; and

5-(2-methoxybenzyl)amino-4-benzhydryl-3-azabicyclo[4.1.0]heptane.

Other compounds of the formula I are:

10-(2-methoxybenzyl)amino-9-phenyl-8-azabicyclo[5.4.0]undecane;

4-(5-t-butyl-2-methoxybenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane;

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- 4-(5-isopropyl-2-methoxybenzyl) amino-3-phenyl-2-
azabicyclo[3.3.0]octane;
- 4-(5-ethyl-2-methoxybenzyl) amino-3-phenyl-2-
azabicyclo[3.3.0]octane;
- 5 4-(2-methoxy-5-n-propylbenzyl) amino-3-phenyl-2-
azabicyclo[3.3.0]octane;
- 4-(5-t-butyl-2-isopropoxybenzyl) amino-3-phenyl-2-
azabicyclo[3.3.0]octane;
- 4-(2-methoxy-5-phenylbenzyl) amino-3-phenyl-2-
10 azabicyclo[3.3.0]octane;
- 4-(5-t-butyl-2-methoxybenzyl) amino-3-diphenylmethyl-2-
azabicyclo[3.3.0]octane;
- 4-(5-t-butyl-2-methoxybenzyl) amino-3-phenyl-2-
azabicyclo[4.4.0]decane;
- 15 4-(5-t-butyl-2-methoxybenzyl) amino-3-diphenylmethyl-2-
azabicyclo[4.4.0]decane;
- 3-diphenylmethyl-4-(5-isopropyl-2-
methoxybenzyl) amino[4.1.0]heptane;
- 9-(5-t-butyl-2-methoxybenzyl) amino-8-phenyl-7-
20 azabicyclo[4.3.0]nonane;
- 10-(5-t-butyl-2-methoxybenzyl) amino-9-phenyl-8-
azabicyclo[5.3.0]nonane;
- 2-aza-4-(5-t-butyl-2-methoxybenzyl) amino-3-phenyl-7-
oxabicyclo[3.3.0]octane;
- 25 2-aza-4-(5-ethyl-2-methoxybenzyl) amino-3-
diphenylmethyl-7-oxabicyclo[3.3.0]octane;
- 2-aza-3-phenyl-4-(2-methoxybenzyl) amino-7-
oxabicyclo[3.3.0]octane;
- 2-aza-3-diphenylmethyl-4-(2-methoxybenzyl) amino-7-
30 oxabicyclo[3.3.0]octane;
- 2-aza-3-phenyl-4-(2-methoxybenzyl) amino-8-
oxabicyclo[3.3.0]octane;
- 2-aza-3-diphenylmethyl-4-(2-methoxybenzyl) amino-8-
oxabicyclo[3.3.0]octane;
- 35 4-(5-5-butyl-2-methoxybenzyl) amino-3-phenyl-2-
azabicyclo[3.3.0]octane;

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- 5-(2-methoxybenzyl) amino-4-phenyl-3-
azabicyclo[5.4.0]undecane;
- 2-(2-methoxybenzyl) amino-3-phenyl-4-
azabicyclo[5.4.0]undecane;
- 5 5-(2-methoxybenzyl) amino-4-phenyl-3-
azabicyclo[5.3.0]undecane;
- 2-(2-methoxybenzyl) amino-3-phenyl-4-
azabicyclo[5.3.0]undecane;
- 4-(2-methoxybenzyl) amino-3-phenyl-2-
10 azabicyclo[4.3.0]nonane;
- 4-(2-methoxybenzyl) amino-3-phenyl-2-
azabicyclo[5.3.0]decane;
- 4-(2-methoxybenzyl) amino-3-phenyl-2-
azabicyclo[5.4.0]undecane;
- 15 4-(2-methoxybenzyl) amino-3-phenyl-2-
azabicyclo[5.5.0]dodecane;
- 9-(2-methoxybenzyl) amino-8-phenyl-7-
azabicyclo[4.3.0]nonane;
- 5-(2-methoxybenzyl) amino-4-phenyl-3-
20 azabicyclo[5.3.0]decane;
- 5-(2-methoxybenzyl) amino-4-phenyl-3-
azabicyclo[4.3.0]nonane;
- 5-(2-methoxybenzyl) amino-4-phenyl-3-
azabicyclo[4.4.0]decane;
- 25 11-(2-methoxybenzyl) amino-10-phenyl-9-
azabicyclo[5.4.0]undecane;
- 5-(2-methoxybenzyl) amino-4-phenyl-3-
azabicyclo[5.1.0]octane;
- 4-(2-methoxybenzyl) amino-3-phenyl-2-aza-8-
30 oxabicyclo[4.3.0]nonane;
- 3-(diphenylmethyl)-4-(2-methoxybenzyl) amino-2-
azabicyclo[3.3.0]octane;
- 5-(2-methoxybenzyl) amino-4-phenyl-3-
azabicyclo[5.4.0]undecane;
- 35 2-(2-methoxybenzyl) amino-3-phenyl-4-
azabicyclo[5.4.0]undecane;

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- 10-(2,5-dimethoxybenzyl)amino-9-phenyl-8-azabicyclo[5.4.0]undecane;
5-(2,5-dimethoxybenzyl)amino-4-phenyl-3-azabicyclo[5.4.0]undecane;
5 2-(2,5-dimethoxybenzyl)amino-3-phenyl-4-azabicyclo[5.4.0]undecane;
5-(2,5-dimethoxybenzyl)amino-4-phenyl-3-azabicyclo[5.3.0]undecane;
2-(2,5-dimethoxybenzyl)amino-3-phenyl-4-azabicyclo[5.3.0]undecane;
10 4-(2,5-dimethoxybenzyl)amino-3-phenyl-2-azabicyclo[4.3.0]nonane;
4-(2,5-dimethoxybenzyl)amino-3-phenyl-2-azabicyclo[5.3.0]decane;
15 4-(2,5-dimethoxybenzyl)amino-3-phenyl-2-azabicyclo[5.4.0]undecane;
4-(2,5-dimethoxybenzyl)amino-3-phenyl-2-azabicyclo[5.5.0]dodecane;
9-(2,5-dimethoxybenzyl)amino-8-phenyl-7-azabicyclo[4.3.0]nonane;
20 5-(2,5-dimethoxybenzyl)amino-4-phenyl-3-azabicyclo[5.3.0]decane;
5-(2,5-dimethoxybenzyl)amino-4-phenyl-3-azabicyclo[4.3.0]nonane;
25 5-(2,5-dimethoxybenzyl)amino-4-phenyl-3-azabicyclo[4.4.0]decane;
11-(2,5-dimethoxybenzyl)amino-10-phenyl-9-azabicyclo[5.4.0]undecane;
5-(2,5-dimethoxybenzyl)amino-4-phenyl-3-azabicyclo[5.1.0]octane;
30 4-(2,5-dimethoxybenzyl)amino-3-phenyl-2-aza-8-oxabicyclo[4.3.0]nonane;
3-(diphenylmethyl)-4-(2,5-dimethoxybenzyl)amino-2-azabicyclo[3.3.0]octane;
35 5-(2,5-dimethoxybenzyl)amino-4-phenyl-3-azabicyclo[5.4.0]undecane;

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- 2-(2,5-dimethoxybenzyl)amino-3-phenyl-4-
azabicyclo[5.4.0]undecane;
- 10-(5-chloro-2-methoxybenzyl)amino-9-phenyl-8-
azabicyclo[5.4.0]undecane;
- 5 5-(5-chloro-2-methoxybenzyl)amino-4-phenyl-3-
azabicyclo[5.4.0]undecane;
- 2-(5-chloro-2-methoxybenzyl)amino-3-phenyl-4-
azabicyclo[5.4.0]undecane;
- 5-(5-chloro-2-methoxybenzyl)amino-4-phenyl-3-
10 azabicyclo[5.3.0]undecane;
- 2-(5-chloro-2-methoxybenzyl)amino-3-phenyl-4-
azabicyclo[5.3.0]undecane;
- 4-(5-chloro-2-methoxybenzyl)amino-3-phenyl-2-
azabicyclo[4.3.0]nonane;
- 15 4-(5-chloro-2-methoxybenzyl)amino-3-phenyl-2-
azabicyclo[5.3.0]decane;
- 4-(5-chloro-2-methoxybenzyl)amino-3-phenyl-2-
azabicyclo[5.4.0]undecane;
- 4-(5-chloro-2-methoxybenzyl)amino-3-phenyl-2-
20 azabicyclo[5.5.0]dodecane;
- 9-(5-chloro-2-methoxybenzyl)amino-8-phenyl-7-
azabicyclo[4.3.0]nonane;
- 5-(5-chloro-2-methoxybenzyl)amino-4-phenyl-3-
azabicyclo[5.3.0]decane;
- 25 5-(5-chloro-2-methoxybenzyl)amino-4-phenyl-3-
azabicyclo[4.3.0]nonane;
- 5-(5-chloro-2-methoxybenzyl)amino-4-phenyl-3-
azabicyclo[4.4.0]decane;
- 11-(5-chloro-2-methoxybenzyl)amino-10-phenyl-9-
30 azabicyclo[5.4.0]undecane;
- 5-(5-chloro-2-methoxybenzyl)amino-4-phenyl-3-
azabicyclo[5.1.0]octane;
- 4-(5-chloro-2-methoxybenzyl)amino-3-phenyl-2-aza-8-
oxabicyclo[4.3.0]nonane;
- 35 3-(diphenylmethyl)-4-(5-chloro-2-methoxybenzyl)amino-
2-azabicyclo[3.3.0]octane;

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- 5-(5-chloro-2-methoxybenzyl) amino-4-phenyl-3-
azabicyclo[5.4.0]undecane;
2-(5-chloro-2-methoxybenzyl) amino-3-phenyl-4-
azabicyclo[5.4.0]undecane;
5 10-(5-fluoro-2-methoxybenzyl) amino-9-phenyl-8-
azabicyclo[5.4.0]undecane;
5-(5-fluoro-2-methoxybenzyl) amino-4-phenyl-3-
azabicyclo[5.4.0]undecane;
2-(5-fluoro-2-methoxybenzyl) amino-3-phenyl-4-
10 azabicyclo[5.4.0]undecane;
5-(5-fluoro-2-methoxybenzyl) amino-4-phenyl-3-
azabicyclo[5.3.0]undecane;
2-(5-fluoro-2-methoxybenzyl) amino-3-phenyl-4-
azabicyclo[5.3.0]undecane;
15 4-(5-fluoro-2-methoxybenzyl) amino-3-phenyl-2-
azabicyclo[4.3.0]nonane;
4-(5-fluoro-2-methoxybenzyl) amino-3-phenyl-2-
azabicyclo[5.3.0]decane;
4-(5-fluoro-2-methoxybenzyl) amino-3-phenyl-2-
20 azabicyclo[5.4.0]undecane;
4-(5-fluoro-2-methoxybenzyl) amino-3-phenyl-2-
azabicyclo[5.5.0]dodecane;
9-(5-fluoro-2-methoxybenzyl) amino-8-phenyl-7-
azabicyclo[4.3.0]nonane;
25 5-(5-fluoro-2-methoxybenzyl) amino-4-phenyl-3-
azabicyclo[5.3.0]decane;
5-(5-fluoro-2-methoxybenzyl) amino-4-phenyl-3-
azabicyclo[4.3.0]nonane;
5-(5-fluoro-2-methoxybenzyl) amino-4-phenyl-3-
30 azabicyclo[4.4.0]decane;
11-(5-fluoro-2-methoxybenzyl) amino-10-phenyl-9-
azabicyclo[5.4.0]undecane;
5-(5-fluoro-2-methoxybenzyl) amino-4-phenyl-3-
azabicyclo[5.1.0]octane;
35 4-(5-fluoro-2-methoxybenzyl) amino-3-phenyl-2-aza-8-
oxabicyclo[4.3.0]nonane;

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3-(diphenylmethyl)-4-(5-fluoro-2-methoxybenzyl)amino-2-azabicyclo[3.3.0]octane;

5-(5-fluoro-2-methoxybenzyl)amino-4-phenyl-3-azabicyclo[5.4.0]undecane; and

5 2-(5-fluoro-2-methoxybenzyl)amino-3-phenyl-4-azabicyclo[5.4.0]undecane.

The present invention also relates to a pharmaceutical composition for treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g.,
10 arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic
15 diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral
20 neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in
25 a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of
30 treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and rhinitis, chronic
35 obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen

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diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, 5 neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, 10 including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition.

The present invention also relates to a pharmaceutical 15 composition for treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and 20 rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy 25 such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to 30 immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of 35 substance P at its receptor site, and a pharmaceutically acceptable carrier.

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The present invention also relates to a method of treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, 5 depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen 10 diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's 15 disease, AIDS related dementia, diabetic enuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising administering to said mammal 20 an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

The present invention also relates to a pharmaceutical 25 composition for antagonizing the effect of substance P at its receptor site in a mammal, including a human, comprising a substance P antagonizing effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

30 The present invention also relates to a method of antagonizing the effect of substance P at its receptor site in a mammal, including a human, comprising administering to said mammal a substance P antagonizing effective amount of a compound of the formula I, or a pharmaceutically 35 acceptable salt thereof.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a

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mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder.

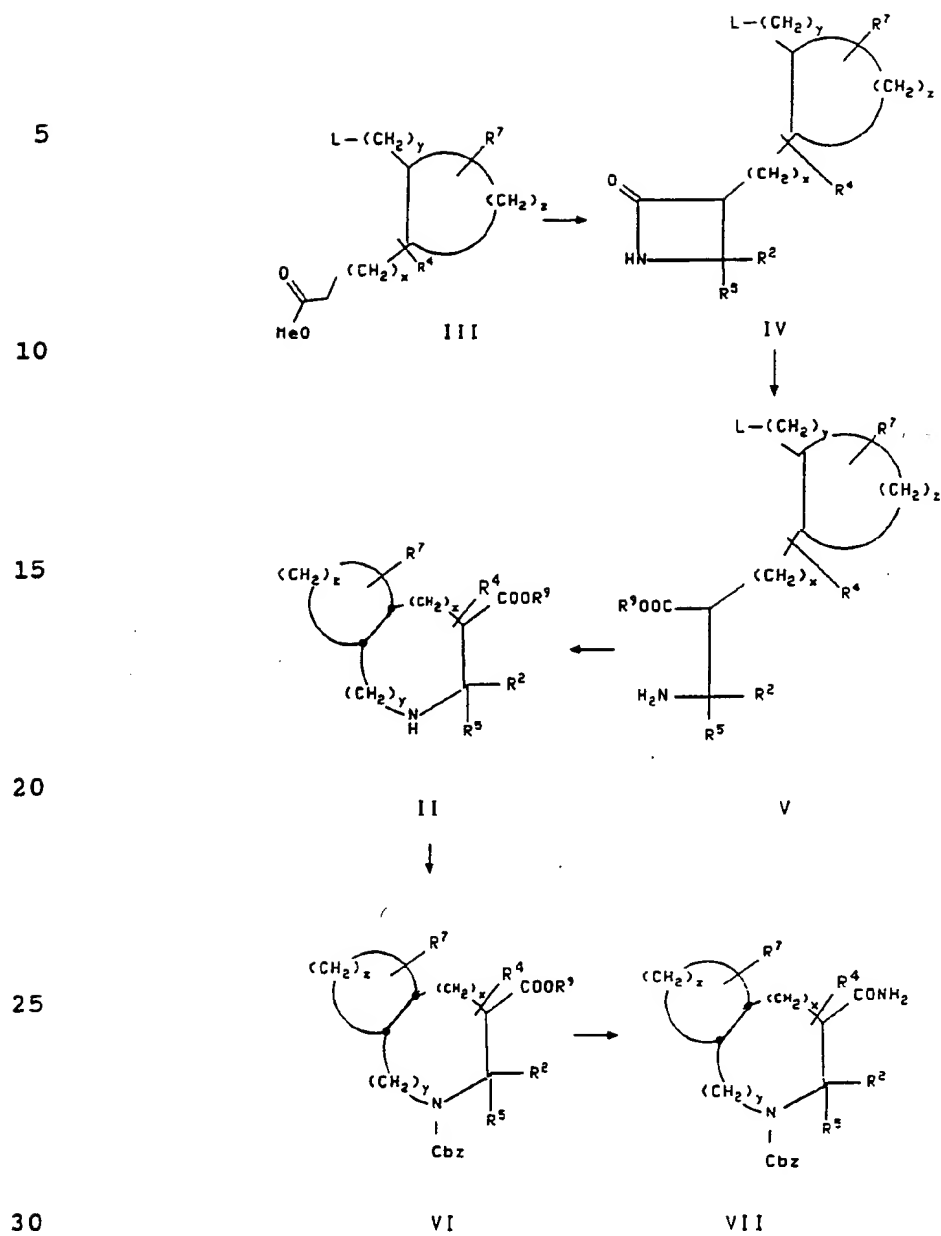
Detailed Description of the Invention

The compounds of the formulae I and II may be prepared as described in the following reaction schemes and discussion. The formulae designated IA, IB, IC and ID represent different classes of compounds having the general

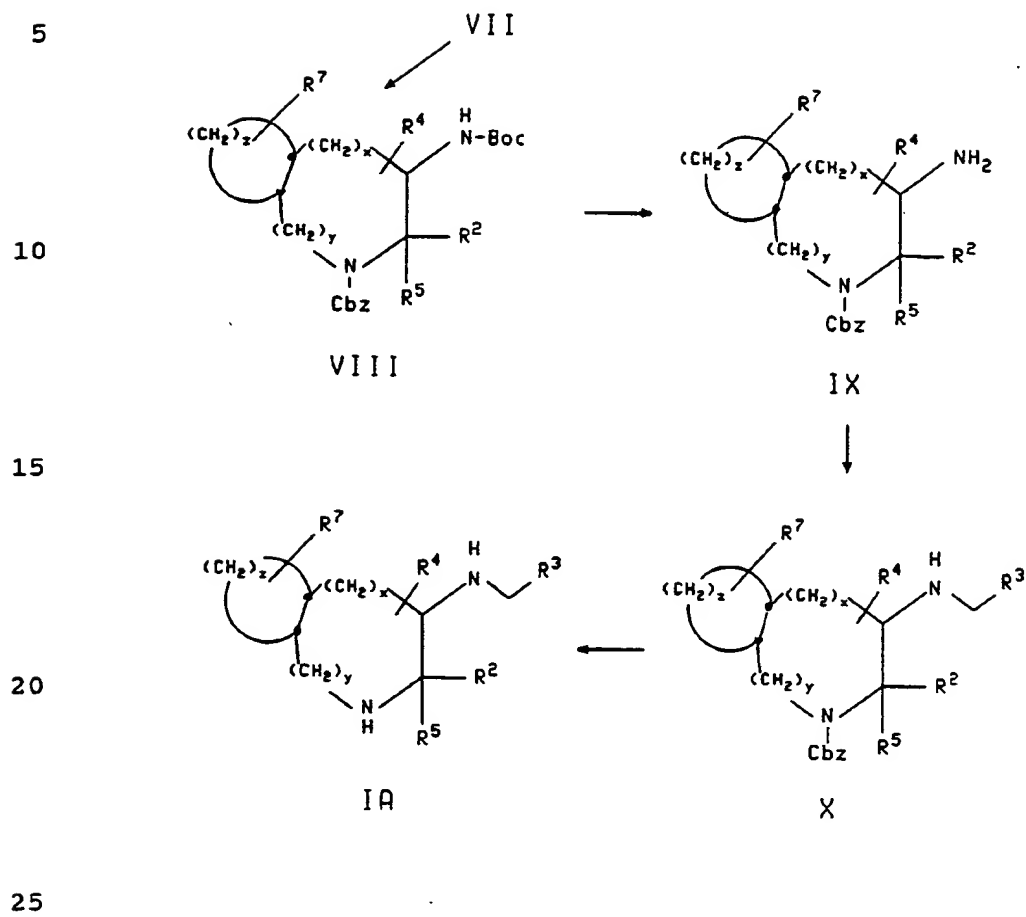
-16-

formula I. Unless otherwise indicated, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , x , y , z and m in the reaction schemes and discussion that follow are defined as above.

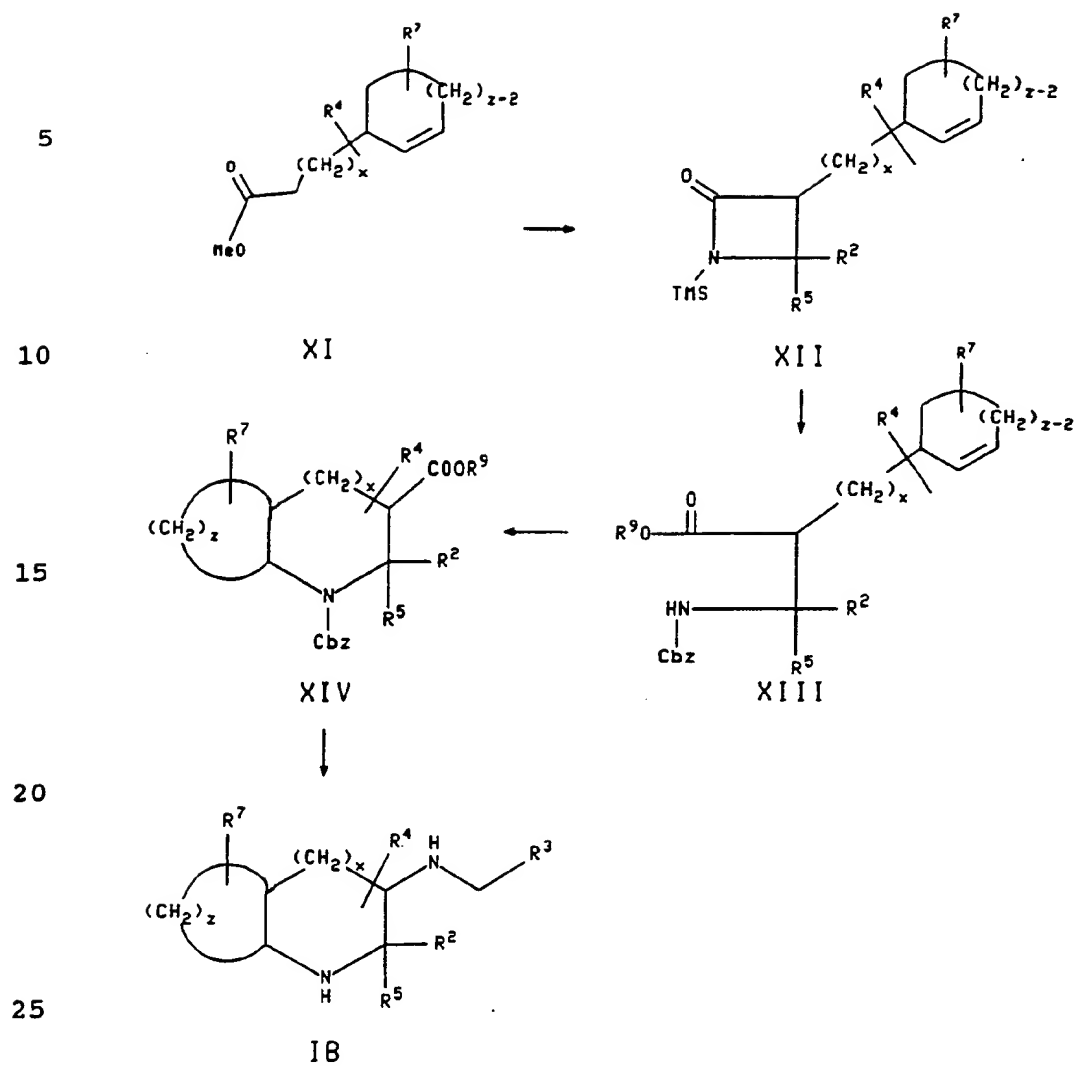
-17-

SCHEME 1

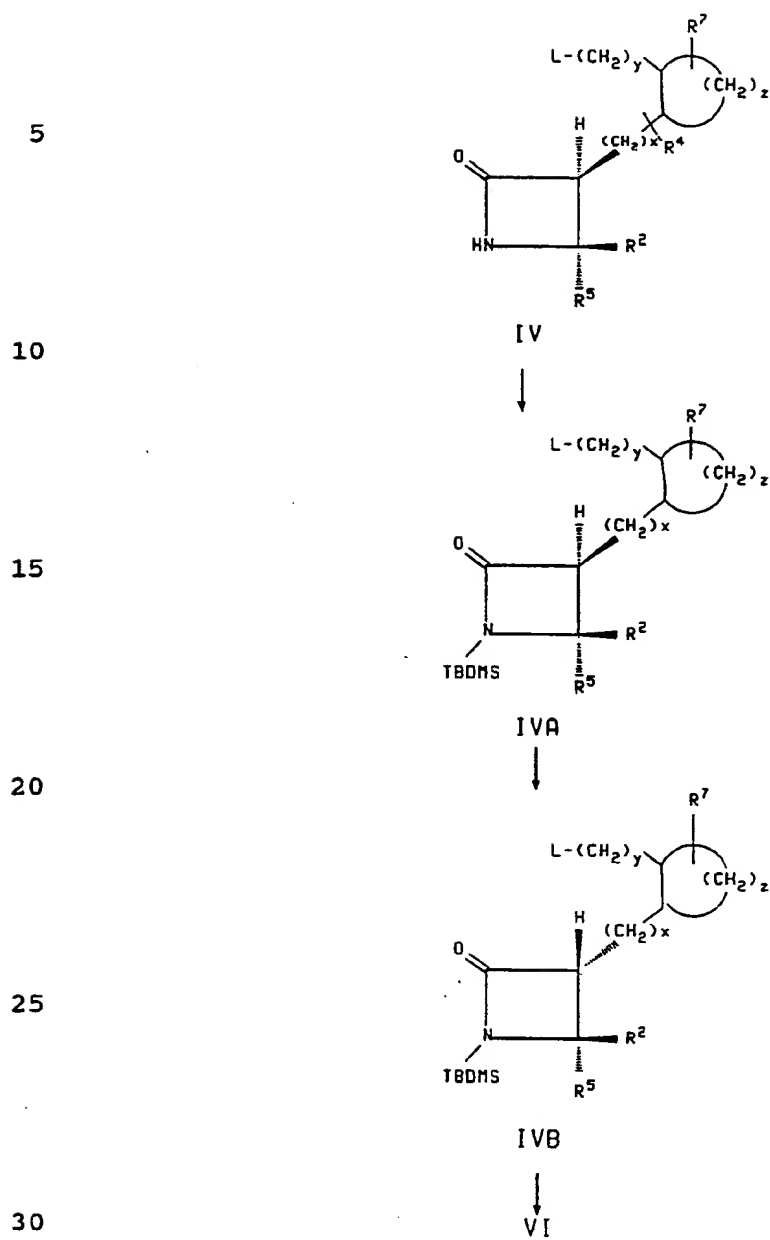
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SCHEME 1 (continued)

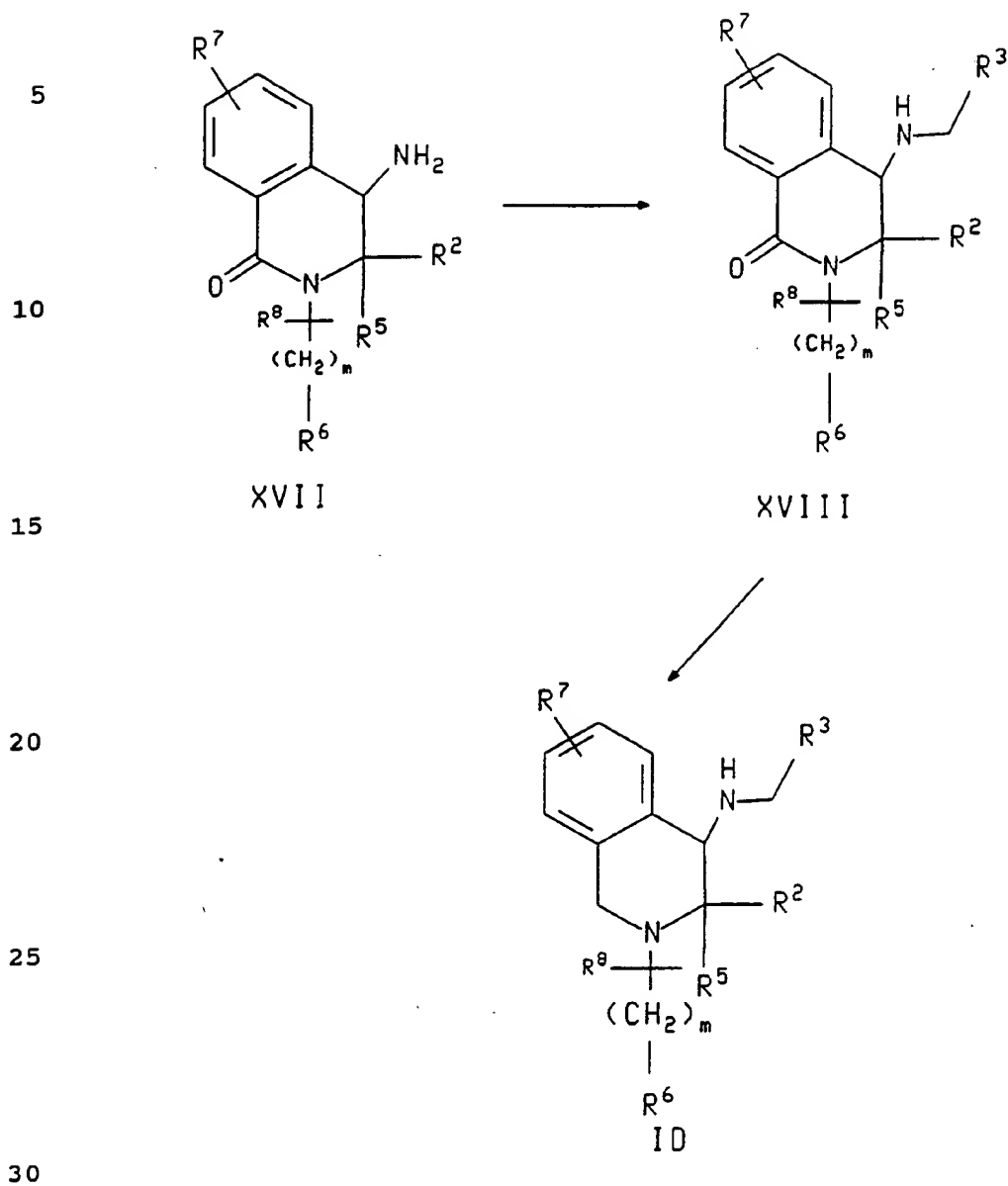
-19-

SCHEME 2

-20-

SCHEME 3

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SCHEME 4

Scheme 1 illustrates the preparation of compounds of
35 the formula IA. Formula IA represents compounds of the
formula I wherein m is zero and both R¹ and R⁶ are hydrogen.

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Referring to scheme 1, a compound of the formula III, wherein L is a leaving group, is reacted with N-(trimethylsilyl)benzalimine. The reaction is generally carried out by adding the compound of formula III in
5 tetrahydrofuran to lithium diisopropylamide-monotetrahydrofuran at a temperature from about -78°C to about -50°C , stirring the resulting mixture for about 0.25 to about 10 hours, and then adding N-(trimethylsilyl)-benzalimine to the mixture at approximately the same
10 temperature over a period of about 5 minutes to about 1 hour. This reaction produces a β -lactam of the formula IV, wherein L is defined as it was for formula III. For example, L may be halo, hydroxy, carbomethoxy or a double bond (i.e., $\text{L} = \text{C}=\text{C}$).

15 Cleavage of the β -lactam with an acid yields a compound of the formula V wherein R^9 is $(\text{C}_1\text{-C}_4)\text{alkyl}$. Typically, this reaction is conducted using a concentrated acid such as concentrated sulfuric or perchloric acid, preferably sulfuric acid, in a polar solvent such as a
20 lower alcohol, preferably methanol, for about 0.5 to about 16 hours. Suitable reaction temperatures range from about room temperature to about 150°C , with the reflux temperature of the solvent being preferred.

The cyclization of the compound of formula V to
25 produce the corresponding compound having formula II is accomplished by heating the crude product of formula V from the foregoing reaction at a temperature from about 80 to about 140°C , preferably at about 100°C , for about 5 minutes to about 2 days, preferably for about 15 minutes, in a high
30 boiling solvent such as dimethylformamide (DMF) or toluene, preferably DMF. This reaction is generally conducted in the presence of sodium iodide, tetrabutylammonium iodide or a similar salt, together with sodium bicarbonate, potassium carbonate or a similar salt. The compound of
35 formula II is then treated with benzylchloroformate in a

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polar solvent such as water, water/acetone, chloroform, dichloroethane or ethyl acetate, in the presence of a base such as triethylamine or sodium bicarbonate, to yield the corresponding N-carbobenzyloxy compound of formula VI

- 5 having the same stereochemistry with respect to the carbons to which R^2 , R^5 and $COOR^9$ are attached. This reaction may be carried out at temperatures from about 0°C to about 100°C, preferably at about 25°C, for about 5 minutes to about 18 hours. Treatment of the compound of formula VI so formed
- 10 with about five equivalents each of trimethyl aluminum and ammonium chloride in a nonpolar solvent such as benzene or toluene for about 0.5 to about 16 hours yields a compound having the formula VII and the same stereochemistry with respect to the carbons to which R^2 , R^5 and $CONH_2$ are
- 15 attached. Reaction temperatures may range from about room temperature to about 100°C. About 50°C is preferred.

- The conversion of the carboxamide group of the compound of formula VII to form a compound of the formula VIII having the same stereochemistry with respect to the
- 20 carbons which R^2 , R^5 and $NHBoc$ are attached ($Boc = t$ -butoxycarbonyl), is generally accomplished by a Hoffmann degradation using lead tetraacetate in t -butanol. This reaction is typically carried out at a temperature from about room temperature to about the reflux temperature of
- 25 the solvent, preferably at about the reflux temperature, for about 15 minutes to about 10 hours, preferably for about 3 to 5 hours. Alternatively, the desired compound of the formula VIII may be obtained via a Hoffman degradation using reagents such as bromine/sodium methoxide in
- 30 methanol, iodobenzene bis(trifluoroacetate) in aqueous acetonitrile, sodium bromide, benzyltrimethyl ammonium tribromide or bis[trifluoroacetoxy]iodobenzene, under the foregoing reaction conditions, followed by treatment of the resulting amine with di- t -butyl dicarbonate. Suitable
- 35 solvents for the above alternative Hoffman degradations include inert aqueous solvents such as tetrahydrofuran (THF), dimethoxythane (DME) and dioxane. The reaction with

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di-tert-butyl dicarbonate is typically conducted in a reaction inert solvent such as dichloromethane or THF at a temperature from about 0°C to about 40°C, preferably at about room temperature.

5 Reaction of the compound of formula VIII with an acid yields a compound of the formula IX having the same stereochemistry with respect to the carbons to which R², R⁵ and NH₂ are attached. Examples of suitable acids are hydrochloric acid, trifluoroacetic acid and perchloric
10 acid. The solvent is typically a polar solvent such as ethyl acetate, methylene chloride, dioxane, ethyl ether or THF, preferably ethyl acetate. This reaction is typically carried out at a temperature from about -10 to about 50°C, preferably at about 25°C, for about 0.5 to about 24 hours.

15 Reductive amination of a compound of the formula R³CHO in the presence of a compound of the formula IX from the above step yields a compound of the formula X having the same stereochemistry. Examples of reducing agents that may be used are hydrogen in the presence of a metal catalyst,
20 sodium borohydride, sodium cyanoborohydride and sodium triacetoxyborohydride. This reaction is generally carried out in a polar solvent such as acetic acid or a lower alkanol, in the presence of a dehydrating agent such as molecular sieves, at a temperature from about 0 to about
25 50°C. Methanol is the preferred solvent and 25°C is the preferred temperature. It is also preferable that the pH of the reaction mixture be about 4 to about 5.

 Alternatively, compounds of the formula X may be formed by acylating a compound of the formula IX with a
30 compound having the formula R³COCl, and then reducing the resulting amide. The acylation is generally conducted in a polar solvent (e.g., dichloromethane, THF or ethyl ether), at a temperature from about 0 to about 60°C. The preferred solvent is dichloromethane and the preferred temperature is
35 about 25°C. Examples of reducing agents that may be used to reduce the amide are lithium aluminum hydride and borane dimethyl sulfide. The reduction is typically carried out

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in a polar solvent (e.g., ether, THF or DME) at a temperature from about 0°C to about the reflux temperature of the solvent, preferably at about room temperature.

The compound of formula X is converted into a compound
5 of the formula IA by reacting it with ammonium formate in the presence of palladium on charcoal (e.g., 10% palladium on charcoal). Usually, a polar solvent such as ethyl acetate or a lower alkanol is used, and the reaction is run at a temperature from about room temperature to about 150°C
10 for about 0.5 to about 24 hours. Preferably, the reaction is conducted in ethanol at room temperature for about 3 to about 24 hours.

The compounds of formula IA prepared by the foregoing procedure may be converted into compounds that are
15 identical but for the fact that R¹ is other than hydrogen as described below. A compound of the formula X is reacted with a compound of the formula R¹X wherein X is a leaving group such as halo (e.g. bromine, chlorine, fluorine, or iodine). This reaction is generally conducted in the
20 presence of a base such as triethylamine or potassium t-butoxide in a polar solvent such as methylene chloride or dichloroethane, at a temperature from about room temperature to about 150°C. Preferably, the reaction is carried out at about the reflux temperature in methylene
25 chloride in the presence of triethylamine. The product of this reaction may be converted to a compound having the formula IA by treatment with ammonium formate in the presence of palladium on charcoal, as described above.

Compounds of the formula IA may be converted into
30 compounds of the formula I that are identical to them but for the fact that R⁶ is other than hydrogen as described below. A compound of the formula IA is reacted with a compound of the formula R⁶-(CH₂)_m-X, wherein X is a leaving group such as halo, wherein one of the carbon-carbon single
35 bonds of said (CH₂)_m may optionally be replaced by a carbon-carbon double bond, and wherein one of the carbons of said (CH₂)_m may optionally be substituted with R⁸. This reaction

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is typically carried out in the presence of a base such as triethylamine or potassium t-butoxide, in a polar solvent such as methylene chloride or dichloroethane, at a temperature from about room temperature to about 150°C.

- 5 Preferably, the reaction is carried out at the reflux temperature in methylene chloride in the presence of triethylamine.

Scheme 2 illustrates an alternate and preferred method of synthesizing compounds of the formula I wherein y is
10 zero, z is greater than one and R⁵ is hydrogen. These compounds are represented in scheme 2 by formula IB.

Referring to scheme 2, a compound of the formula XI is reacted with a compound having the formula



wherein R⁵ is hydrogen. This reaction is generally carried
20 out by adding the compound of formula XI in tetrahydrofuran to lithium diisopropylamide monotetrahydrofuran at a temperature from about -78°C to about -50°C, stirring the resulting mixture for about 0.25 to about 10 hours, and then adding the compound of formula XXVI to the mixture at
25 approximately the same temperature over a period of about 5 minutes to about 1 hour. This reaction produces a β-lactam of the formula XII.

Cleavage of the β-lactam with an acid followed by treatment with benzylchloroformate yields a compound of the
30 formula XIII having the same stereochemistry, wherein R⁹ is (C₁-C₄)alkyl. Cleavage of the β-lactam is typically conducted using a concentrated acid such as concentrated sulfuric or perchloric acid, preferably sulfuric acid, in a polar solvent such as a lower alcohol, preferably methanol,
35 for about 0.5 to about 16 hours. Suitable reaction temperatures range from about room temperature to about 150°C, with the reflux temperature of the solvent being

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preferred. The product of this reaction is a compound having a structure similar to that of formula XIII, except that the N-carbobenzyloxy group is replaced by hydrogen. Treatment of this compound with benzylchloroformate to
5 produce a compound of the formula XIII having the same stereochemistry is generally carried out in a polar solvent such as water, water/acetone, chloroform, dichloroethane or ethyl acetate in the presence of a base. Examples of bases that may be used are triethylamine, sodium bicarbonate and
10 potassium bicarbonate. This reaction may be conducted at temperatures from about 0°C to about 100°C, for a period of about 5 minutes to about 18 hours. Preferably, it is conducted at about 25°C.

The compound of formula XIII may be cyclized to form
15 the corresponding compound having the formula XIV and the same stereochemistry with respect to the carbons to which R², R⁵ and COOR⁹ are attached, by first reacting it with mercuric trifluoroacetate, mercuric chloride or mercuric acetate, and then reacting the product of such reaction
20 with sodium borohydride, lithium triacetoxyborohydride or a similar reducing agent. The reaction with the mercury salt is usually conducted in a polar solvent at a temperature from about -78°C to about 25°C. Suitable solvents include THF, acetonitrile and nitromethane. The reaction is
25 carried out preferably using mercuric trifluoroacetate in THF at about 25°C. The reaction with sodium borohydride is generally carried out by adding an aqueous solution of sodium borohydride to the reaction mixture from the foregoing reaction at a temperature from about -78°C to
30 about 0°C, preferably at about 0°C.

Compounds of the formula XIV may be converted to the corresponding compounds having the formula IB and the same stereochemistry with respect to the carbons to which R², R⁵ and NHR³ are attached by the method illustrated in scheme 1
35 and described above for converting compounds of the formula VI into compounds of the formula IA.

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Compounds of the formula I may also be prepared using the procedure described in Example 8.

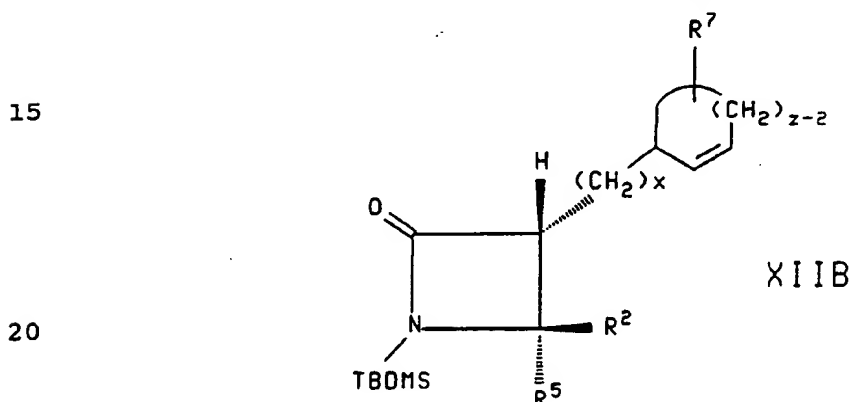
Scheme 3 illustrates a variation of scheme 1 that may be used to obtain compounds of the formula IA wherein R⁵ is hydrogen having a particular stereochemistry. Referring to scheme 3, the β -lactam of formula IV, which is produced in the first reaction of scheme 1, is reacted with t-butyldimethylsilyl (TBDMS) triflate. The reaction is typically conducted in a polar, reaction inert solvent in the presence of a hindered tertiary amine such as diisopropylethyl amine at a temperature from about -78°C to about 50°C. It is preferably conducted at about 0°C. Suitable solvents include methylene chloride, ether, THF and ethyl acetate, with methylene chloride being preferred. The product of this reaction is a compound of the formula IVA. This compound may be converted to the corresponding compound having the formula IVB by reacting it first with lithium diisopropylamide and then with a weak organic or inorganic acid. Generally, the reaction with lithium diisopropylamide is carried out in a reaction inert solvent such as THF, ether or DME, preferably THF, at a temperature from about -78°C to about 0°C, preferably at about -78°C. The reaction with a weak acid is generally accomplished by quenching the mixture from the above reaction with acetic acid, ethanol/methanol, water, aqueous ammonium chloride or trifluoroacetic acid, preferably acetic acid, in a reaction inert solvent such as THF, ether or hexane, preferably THF, at a temperature from about -78°C to about 0°C. A temperature of about 25°C is preferred.

The compounds of the formula IVB produced by the procedure of scheme 3 will have a stereochemistry opposite to that of the corresponding compounds of the formula IVA from which they were made, with respect to the carbon to which R² and R⁵ are attached and the carbon adjacent to it. These compounds of formula IVB may then be converted to the corresponding compounds of the formula IA by the procedure illustrated in scheme 1 and described above for converting

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compounds of the formula IV to compounds of the formula IA. By using the procedure of scheme 3 in combination with that of scheme 1, as described above, compounds of the formula IA having the cis configuration may be formed from the
 5 corresponding compounds of the formula IV having the cis configuration.

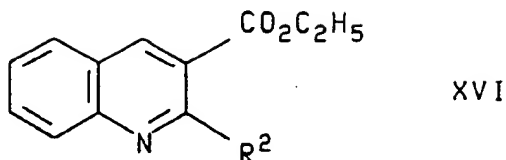
Similarly, the procedure of scheme 3 may be used in combination with the procedure of scheme 2 to produce compounds of the formula IB having a particular
 10 stereochemistry. Thus, compounds of the formula XII, as shown in scheme 2, having the cis configuration may be converted to the corresponding compounds of the formula



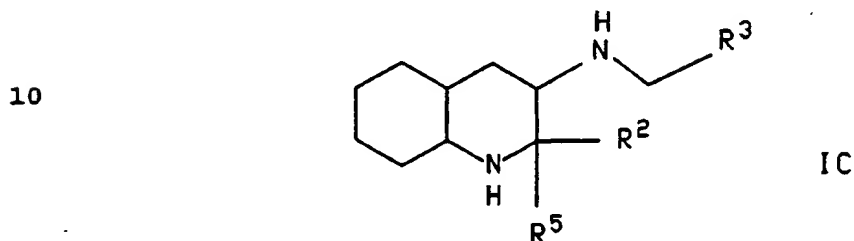
wherein R⁵ is hydrogen by a method analogous to the procedure described above for forming compounds of the
 25 formula IVB from compounds of the formula IV. The compounds of formula XIIB so formed may then be converted into the corresponding compounds of the formula IB having the same stereochemistry using the procedure illustrated in scheme 2 and described above for forming compounds of the
 30 formula IB from compounds of the formula XII.

An alternate and preferred method of synthesizing compounds of the formula I wherein m and y are zero, x is one, z is four, R¹ and R⁶ are both hydrogen, and the (CH₂)_z containing ring is saturated (hereinafter referred to as
 35 compounds of the formula IC) involves reducing a compound of the formula

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5 using hydrogen in the presence of an acid and a metal catalyst, and then converting the derived compound to a compound of the formula



10 using the series of reactions illustrated in scheme 1 and described above for effecting the following transformations: II→VI→VII→IX→X→IA. The reduction of the compound having formula XVI is usually conducted using platinum oxide, platinum on carbon or palladium on carbon as the catalyst and acetic acid or hydrochloric acid/alcohol as the acid. Preferably, platinum oxide and acetic acid are used.

25 Scheme 4 depicts an alternate and preferred method of synthesizing compounds of the formula I wherein R¹ is hydrogen, z is 4, y is 1 and x is 0. These compounds are represented by formula ID in scheme 4.

Referring to scheme 4, a compound of XVII is converted into the corresponding compound having formula XVIII by a reductive amination using the procedure described above for forming compounds of the formula X from compounds of the formula IX.

30 Reduction of either the cis or trans isomer of the compound of formula XVIII, or a mixture thereof, yields a compound of the formula ID having the same stereochemistry. Reducing agents such as lithium aluminum hydride, borane in THF and sodium borohydride-titanium (IV) chloride are suitable; however, best results are obtained by using borane dimethylsulfide in THF. The reaction may be carried

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out at temperatures from about room temperature to about 150°C. It is preferably carried out at the reflux temperature of the solvent.

Compounds identical to those of the formulae IB, IC
5 and ID but for the fact that R¹ or R⁶ is other than hydrogen may be prepared from the corresponding compounds of the formulae IB, IC and ID by the methods described above for synthesizing compounds identical to those of formula IA but for the fact that R¹ or R⁶ is other than hydrogen.

10 The preparation of other compounds of the formula I not specifically described above can be accomplished using combinations of the above reactions that will be clear to those skilled in the art in view of the foregoing disclosure.

15 In each of the reactions discussed or illustrated in schemes 1 to 4 above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, and ambient pressure, i.e. about 1 atmosphere, is preferred as
20 a matter of convenience.

The compounds of the formula I and the pharmaceutically acceptable salts thereof (hereinafter referred to as the active compounds) are useful as substance P antagonists, i.e., they possess the ability to
25 antagonize the effects of substance P at its receptor site in mammals, and therefore are able to function as therapeutic agents in the treatment of the aforementioned disorders and diseases in an afflicted mammal.

The compounds of the formula I which are basic in
30 nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I
35 from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline

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reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

10 The compounds of formula I and their pharmaceutically acceptable salts exhibit substance P receptor-binding activity and therefore are of value in the prevention and treatment of a wide variety of clinical conditions the treatment or prevention of which is effected or facilitated
15 by a decrease in substance P mediated neurotransmission. Such conditions include inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and
20 rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy
25 such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to
30 immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis. Hence, these compounds are readily adapted to therapeutic use as substance P antagonists for the control and/or treatment of any of the aforesaid clinical conditions in
35 mammals, including humans.

 The compounds of the formula I and the pharmaceutically acceptable salts thereof can be

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administered via the oral, parenteral or topical routes. In general, these compounds are most desirably administered in dosages ranging from about 5.0 mg up to about 1500 mg per day, although variations will necessarily occur

5 depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.07 mg to about 21 mg per kg of body weight per day is most desirably employed. Variations may nevertheless

10 occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the

15 lower limit of the aforesaid range may be more than adequate while in other cases still larger doses may be employed without causing any harmful side effect provided that such higher dose levels are first divided into several small doses for administration throughout the day.

20 The active compounds of this invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the three routes previously indicated, and such administration can be carried out in single or multiple doses. More

25 particularly, the active compounds of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, aerosols,

30 creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solids diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover,

35 oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compounds of this

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invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium
5 citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with
10 granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this
15 connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or
20 dyes, and, if desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

For parenteral administration, solutions of a
25 therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for
30 intravenous injection purposes. The oily solutions are suitable for intraarteriolar, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well-
35 known to those skilled in the art. Additionally, it is also possible to administer the compounds of the present invention topically when treating inflammatory conditions

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of the skin. This may be done, preferably, by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

The activity of the compounds of the present invention as substance P antagonists may be determined by their ability to inhibit the binding of substance P at its receptor sites in bovine caudate or other mammalian tissue, employing radioactive ligands to visualize the tachykinin receptors by means of autoradiography. The substance P antagonist activity of the herein described compounds may be evaluated using the standard assay procedure described by M.A. Cascieri *et al.*, as reported in the Journal of Biological Chemistry, Vol. 258, p. 5158 (1983) or variations thereof. This method essentially involves determining the concentration of the individual compound required to reduce by 50% the amount of radiolabelled substance P ligands at their receptor sites in said isolated cow or other mammalian tissues, thereby affording characteristic IC_{50} values for each compound tested.

In one procedure, bovine caudate tissue is removed from a $-70^{\circ}C$ freezer and homogenized in 50 volumes (w./v.) of ice cold 50 Mm Tris (i.e., 2-amino-2-hydroxymethyl-1,3-propanediol) hydrochloride buffer having a pH of 7.7. The homogenate is centrifuged at $30,000 \times G$ for a period of 20 minutes. The pellet is resuspended in 50 volumes of Tris buffer, rehomogenized and then recentrifuged at $30,000 \times G$ for another twenty minute period. The pellet is then resuspended in 40 volumes of ice-cold 50 Mm Tris buffer (pH 7.7) containing 2 mM of calcium chloride, 2 mM of magnesium chloride, 40 g/ml of bacitracin, $4\mu g/ml$ of leupeptin, $2\mu g$ of chymostatin and 200 g/ml of bovine serum albumin. This step completes the production of the tissue preparation.

The radioligand binding procedure is then carried out by initiating the reaction via the addition of 100 μl of the test compound made up to a concentration of $1\mu M$, followed by the addition of 100 μl of radioactive ligand made up to a final concentration 0.5 mM and then finally by

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the addition of 800 μ l of the tissue preparation produced as described above. The final volume is 1.0 ml. The reaction mixture is then vortexed and incubated at room temperature (ca. 20°C) for a period of 20 minutes. The tubes are then filtered using a cell harvester, and the glass fiber filters (Whatman GF/B) are washed four times with 50 mM Tris buffer (pH 7.7), the filters having previously been presoaked for a period of two hours prior to the filtering procedure. Radioactivity is then determined in a Beta counter at 53% counting efficiency, and the IC₅₀ values calculated using standard statistical methods.

The antipsychotic activity of the compounds of the present invention as neuroleptic agents for the control of various psychotic disorders is determined primarily by a study of their ability to suppress substance P-induced or substance P agonist induced hypermotility in guinea pigs. This study is carried out by first dosing the guinea pigs with a control compound or with an appropriate test compound of the present invention, then injecting the guinea pigs with substance P or a substance P agonist by intracerebral administration via canula and thereafter measuring their individual locomotor response to said stimulus.

The present invention is illustrated by the following examples. However, the invention is not limited to the specific details of these examples.

EXAMPLE 1

[1 α ,3 α ,4 α ,5 α]-4-(2-Methoxybenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane

A. Cis-3-(2-cyclopentenyl)-4-phenyl-1-azetidin-2-one

To a cooled solution of lithium bis(trimethylsilyl)amide (1.0M in tetrahydrofuran, 200 mL, 200 mmoles) at -78°C was added benzaldehyde (19.7 gms, 189 mmoles). The reaction mixture was warmed to 0°C for 30 mins and recooled to -78°C. In another flask lithium diisopropylamide-monotetrahydrofuran (1.5M in cyclohexanes,

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114 mL, 171 mmole) in tetrahydrofuran (150 ml) was cooled to -78°C and to it a solution of 2-cyclopentene-1-acetic acid, methyl ester (20 g, 142.8 mmole) in tetrahydrofuran (150 mL) was added slowly. The reaction mixture was
5 stirred for 30 minutes at -78°C followed by the addition of the contents of the first flask via cannula over a 15 minute period. The cold bath was removed and the mixture was allowed to warm to room temperature (1.5 hours.) The resulting solution was diluted with 100 mL 1N HCl and
10 stirred for 1 hour. The resulting solution was extracted with ether (3 x 350 mL). The organic phases were combined and washed with water, dried (anhydrous MgSO₄) and concentrated in vacuo to afford a residue which on trituration with ether-pentane afforded the desired β-
15 lactam as white solid (20.6 gms). The mother liquor was concentrated and chromatographed. Elution with 30% ethyl acetate in hexane afforded additional cis-3-(2-cyclopentenyl)-4-phenyl-1-azetidin-2-one (4.14 gms, total yield 81%).

20 ¹H NMR δ (CDCl₃) 1.03-1.15 (1H, m), 1.16-1.3 (1H, m), 1.8-2.3 (2H, m), 2.55-2.75 (1H, m), 3.23-3.48 (1H, m), 4.88 (1H, d, J=5.3 Hz), 4.95-5.05 (0.33H, m), 5.55-5.63 (0.33H, m), 5.64-5.7 (0.66H, m), 5.85-5.92 (0.66H, m), 6.1 (1H, bd), 7.2-7.4 (5H, m).

25 B. Cis-3-(2-cyclopentenyl)-4-phenyl-1-(tert.-butyldimethylsilyl)azetidin-2-one

To a stirred solution of cis-3-(2-cyclopentenyl)-4-phenyl-1-azetidin-2-one (24.73 g, 116 mmoles), and diisopropylethyl amine (26.3 mL, 150 mmoles) in methylene
30 chloride (400 mL) at 0°C, was added tert. butyldimethylsilyl triflate (31.5 mL, 139 mmoles). The reaction mixture was stirred for 15 minutes, and was then diluted with methylene chloride (200 ml) and with water. The organic phase was successively washed with 1N HCl
35 (1 x 100 ml), 1N NaHCO₃ (1 x 100 ml) and water (2 x 100 mL). The methylene chloride layer was dried (anhydrous MgSO₄), filtered and concentrated under vacuum to afford pure cis-

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3-(2-cyclopentenyl)-4-phenyl-1-(tert.-
butyldimethylsilyl)azetidin-2-one (33.76 gm, 89%).

¹H NMR δ (CDCl₃) 0.68 (3H, s), 0.95 (9H, s), 0.95-1.15
(2H, m), 1.8-2.15 (2H, m), 2.53-2.72 (1H, m), 3.3-3.4 (1H,
5 m), 4.7 (1H, d, J=4Hz), 4.73-4.8 (0.33H, m), 5.5-5.57
(0.33H, m), 5.6-5.7 (0.66H, m), 5.9-6.0 (0.66H, m), 7.3-
7.45 (5H, m).

C. Trans-3-(2-cyclopentenyl)-4-phenyl-1-(tert.-
butyldimethylsilyl)azetidin-2-one

10 To a stirred solution of cis-3-(2-cyclopentenyl)-4-
phenyl-1-(tert-butyldimethylsilyl)azetidin-2-one (15.00
gms, 46 mmoles) in tetrahydrofuran (200 mL) at -78°C, was
added lithium diisopropylamide in tetrahydrofuran (1.5M,
33.6 mL, 50 mmoles). The reaction mixture was then warmed
15 to -50°C and stirred for 20 minutes. At the end of this
period the reaction mixture was quenched with acetic acid
(13.7 gms, 228 mmoles) in tetrahydrofuran (50 mL) and was
warmed to room temperature (25°C). Thereafter, it was
concentrated under vacuum, diluted with 1N HCl and
20 extracted with ethyl ether (3 x 150 ml). The combined
organic layers were washed with water (2 x 100 mL), dried
(anhydrous MgSO₄) and filtered. The ethyl ether was
removed under vacuum to afford an orange colored oil (17.5
g) which was loaded on flash silica gel column. Elution
25 with 10% ethyl acetate in hexane afforded pure trans-3-(2-
cyclopentenyl)-4-phenyl-1-(tert-
butyldimethylsilyl)azetidin-2-one (6.86 gms, 46%).

¹H NMR (CDCl₃) δ 0.19 (3H, s), 0.91 (9H, s), 1.5-1.65
(1H, m), 2.0-2.15 (1H, m), 2.3-2.5 (2H, m), 3.1-3.25 (2H,
30 m), 4.19 (1H, d, J=2.4 Hz), 5.65-5.75 (1H, m), 5.85-5.95
(1H, m), 7.23-7.4 (5H, m).

D. Methyl 2-(2-cyclopentenyl)-3-phenyl-3-
(benzyloxycarbonyl)amino-propionate

A solution of trans-3-(2-cyclopentenyl)-4-phenyl-1-
35 (tert-butyldimethylsilyl)azetidin-2-one (9.18 gms, 28
mmoles) in 5% sulfuric acid in methanol was refluxed for 18
hours. At the end of this period the reaction mixture was

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cooled and carefully neutralized with powdered sodium bicarbonate. The contents of the flask were concentrated under vacuum and, after dilution with water (200 mL), were extracted with methylene chloride (3 x 150 mL). The combined organic layers were dried (anhydrous MgSO_4) and filtered. The solvents were removed under vacuum to afford hydrolyzed product as an orange tinted solid (6.61 gms, 100%) which was dissolved in ethyl acetate (70 mL) and cooled to 0°C. To it an aqueous potassium carbonate solution (2M, 67.4 mL, 135 mmole) and benzyl chloroformate (11.4 gms, 30 mmole) were added. The reaction mixture was warmed to room temperature and the aqueous layer was extracted with additional ethyl acetate (2x100 mL). The combined organic layers were dried (anhydrous MgSO_4), filtered and concentrated under vacuum to afford methyl 2-(2-cyclopentenyl)-3-phenyl-3-(benzyloxycarbonyl)amino-propionate (11.6 gms, 100%).

^1H NMR (CDCl_3) δ 1.5-1.65 (1H, m), 1.85-2.05 (1H, m), 2.0-2.5 (2H, m), 2.66 (1H, dd $J=10, 4$ Hz), 3.0-3.15 (1H, m), 3.45 (3H, s), 5.1 (2H, bs), 5.87 (1H, s), 6.45 (1H, bd, $J=9.4$ Hz), 7.1-7.5 (10H, m).

E. [1 α ,3 α ,4 α ,5 α]-2-(Benzyloxycarbonyl)-3-phenyl-2-azabicyclo[3.3.0]octane-4-carboxylic acid, methyl ester

To a stirred solution of methyl 2-(2-cyclopentenyl)-3-phenyl-3-(benzyloxycarbonyl)amino-propionate (10.21 gms, 27 mmole) in tetrahydrofuran (60 mL) at 0°C, a solution of mercuric trifluoroacetate (16.0 gms, 38 mmole) in tetrahydrofuran (65 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 15 minutes. The reaction mixture was recooled to 0°C and to it a solution of sodium borohydride (4.1 gms, 108 mmole) in water (40 mL) was added slowly; it was stirred for 30 minutes during which time grey precipitates were formed. At the end of this period the reaction mixture was filtered through diatomaceous earth (Celite (trademark)) and the filtrate was concentrated under vacuum. The residue was suspended

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in water and extracted with methylene chloride (3 x 100 ml). The combined organic layers were dried (anhydrous MgSO_4), filtered and concentrated under vacuum to afford [1 α ,3 α ,4 α ,5 α]-2-(benzyloxycarbonyl)-3-phenyl-2-azabicyclo[3.3.0]octane-4-carboxylic acid, methyl ester (10.9 gms, 100%) as a solid.

F. [1 α ,3 α ,4 α ,5 α]-2-(Benzyloxycarbonyl)-4-carboxamide-3-phenyl-2-azabicyclo[3.3.0]octane

To a suspension of the ammonium chloride (4.23 gm, 79 mmole) in benzene (40 ml) at 5°C, was slowly added a 2M solution (39.5 ml, 79 mmole) of trimethyl aluminum in hexane. After addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred for 45 min. until gas evolution had ceased. To it a solution of [1 α ,3 α ,4 α ,5 α]-2-(benzyloxycarbonyl)-3-phenyl-2-azabicyclo[3.3.0]octane-4-carboxylic acid, methyl ester (6.0 gm, 16 mmole) in benzene (50 ml) was added and the solution was maintained at 50°C for 16 hours. The reaction mixture was cooled to room temperature and was carefully quenched with 5% HCl. Then the resulting mixture was filtered through diatomaceous earth (Celite (trademark)) and the residue was washed with methylene chloride (200 ml). The organic layer was separated while the aqueous layer was made basic and extracted with methylene chloride (200 ml). The organic extracts were combined, dried (anhydrous MgSO_4) and concentrated in vacuo to afford a residue which was suspended in 1:1 ether-pentane to afford [1 α ,3 α ,4 α ,5 α]-2-benzyloxycarbonyl)-4-carboxamide-3-phenyl-2-azabicyclo[3.3.0]octane as white solid (2.91 gm, 50%).

^1H NMR δ (CDCl_3) 1.5-2.2 (6H, m), 2.9-3.2 (2H, m), 4.4-4.6 (1H, m), 4.7-5.4 (5H, m), 6.77 (1H, d, $J=6.5$ Hz), 7.0-7.4 (9H, m).

G. [1 α ,3 α ,4 α ,5 α]-4-Amino-2-(benzyloxycarbonyl)-3-phenyl-2-azabicyclo[3.3.0]octane

To a slurry of [1 α ,3 α ,4 α ,5 α]-2-(benzyloxycarbonyl)-4-carboxamide-3-phenyl-2-azabicyclo[3.3.0]octane (2.84 gms, 7.8 mmole) in acetonitrile (30 mL) and water (30 mL) was

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added bis[(trifluoroacetoxy)iodo]benzene. The reaction mixture was stirred for 2 days at room temperature and then poured into ether (200 mL). The ether layer was extracted with 1N HCl (2 x 100 mL). The combined acidic layers were
5 made alkaline with 10% ammonium hydroxide and extracted with methylene chloride (3 x 100 ml). The combined methylene chloride layers were dried (anhydrous MgSO₄), filtered and concentrated under vacuum to afford [1 α ,3 α ,4 α ,5 α]-4-amino-2-(benzyloxycarbonyl)-3-phenyl-2-azabicyclo[3.3.0]octane as
10 an oil (1.25 gms, 47%).

¹H NMR (CDCl₃) δ 1.4-1.9 (1H, m), 1.95-2.1 (1H, m), 2.25-2.4 (1H, m), 3.2-3.4 (1H, m), 4.5-4.55 (1H, m), 4.7-5.1 (3H, m), 6.76 (1H, d, J=6.2 Hz), 7.0-7.4 (9H, m).

H. [1 α ,3 α ,4 α ,5 α]-4-(2-Methoxybenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane
15

[1 α ,3 α ,4 α ,5 α]-4-Amino-2-(benzyloxycarbonyl)-3-phenyl-2-azabicyclo[3.3.0]octane (0.532 gm, 1.6 mmole) was dissolved in methanol (20 ml) and the pH of the medium was adjusted to 5 with methanolic HCl. To it crushed 4A° molecular sieves
20 (1.0 gm), sodium cyanoborohydride (0.102 gm, 1.6 mmole) and o-methoxy benzaldehyde (0.258 gm, 1.90 mmole) was added and the resulting reaction mixture was stirred at room temperature for 16 hours. At the end of this period the reaction mixture was filtered through diatomaceous earth
25 (Celite (trademark)) and the filtrate was taken up in aqueous ammonium hydroxide. The aqueous phase was extracted with methylene chloride (3 x 60 ml) and dried (anhydrous MgSO₄). The solvents were removed under reduced pressure to afford an oily residue (0.813 gm). The residue was loaded on
30 a short silica gel column. Elution with 30% ethyl acetate in hexane afforded product (0.617 g). The product was dissolved in ethanol (20 ml) and to it 10% palladium on carbon (1.2 gm) and ammonium formate (0.864 gm, 14 mmole) were added. The resulting reaction mixture was stirred at
35 25°C for 16 hours. At the end of this period the reaction mixture was filtered through diatomaceous earth (Celite (trademark)) which was washed with ethanol (50 ml) and

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methylene chloride (100 ml). The solvents were removed under vacuum to afford a solid which was taken up in aqueous ammonium hydroxide and extracted with methylene chloride (3 x 60 ml). The organic extracts were combined and dried (anhyd. MgSO₄). Evaporation of the solvents under reduced pressure afforded a yellow oil (441 mg) from which [1 α ,3 α ,4 α ,5 α]-4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane (403 mg, 83%) was isolated as a white solid by treatment with ether-HCl. This was crystallized from ethanol/methanol to afford crystalline [1 α ,3 α ,4 α ,5 α]-4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane hydrochloride (111 mg, 18%, m.p. 250°C). The structure was further confirmed by single crystal X-ray crystallographic analysis.

¹H NMR (CDCl₃) δ 1.2-1.55 (2H, m), 1.6-1.75 (1H, m), 1.8-2.1 (3H, m), 2.6 (1H, dd, J=16, 8Hz), 2.91 (1H, dd, J=4.5, 1.5 Hz), 3.51 (3H, s), 3.51 (1H, d, J=13.5 Hz), 3.75 (1H, d, J=13.5 Hz), 4.03 (1H, dd, J=13.6, 8 Hz), 4.27 (1H, d, J=4.5 Hz), 6.74 (1H, d, J=8 Hz), 6.84 (1H, dt, J=7.5 Hz), 7.03 (1H, d, J=7.5 Hz), 7.1-7.35 (6H, m).

¹³C-NMR (CDCl₃) δ 25.9, 31.5, 35.3, 47.2, 48.6, 54.8, 62.5, 64.3, 67.5, 109.0, 120.1, 126.7, 127.2, 128.0, 128.1, 128.3, 130, 139.1, 157.7.

EXAMPLE 2

4-(2-Methoxybenzyl)amino-3-phenyl-2-azabicyclo[4.4.0]decane
A. 3-Carboethoxy-2-phenylquinoline

Under a nitrogen atmosphere, in a round-bottom flask equipped with a pressure-equalizing addition funnel was placed 3.7 mL (47 mmol) of DMF, and the system was placed in an ice bath. To this stirring liquid was added dropwise 8.4 mL (89 mmol) of POCl₃. The mixture was warmed to 25°C using a warm water bath and stirred at room temperature for 0.5 hours. The system was cooled in an ice bath, and 12.0 g (44.9 mmol) of 2-carboethoxy-1-phenyl-1-(phenylamino)ethene in 45 mL of 1,1,2,2-tetrachloroethane was added dropwise to the system. The mixture was heated at 80°C for 3 hours, cooled and added slowly to iced water.

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The mixture was made basic with saturated aqueous NaHCO_3 and extracted with two portions of CHCl_3 . The combined organic fractions were washed with two portions of H_2O , dried (Na_2SO_4) and concentrated in vacuo to obtain 18.4 g of oil. This material was purified by flash column chromatography, gradually increasing the polarity of the eluant from hexanes to 8:1 hexanes/ethyl acetate, to obtain 5.2 g of the title compound.

^1H NMR (CDCl_3) δ 1.08 (t, 3H, $J=8$), 4.18 (q, 2H, $J=8$), 7.40-7.68 (m, 1H), 7.93 (d, 1H, $J=10$), 8.19 (d, 1H, $J=10$), 8.63 (s, 1H).

B. 4-Carboethoxy-3-phenyl-2-azabicyclo[4.4.0]decane

3-Carboethoxy-2-phenylquinoline (1.5 g, 5.4 mmol), 150 mg of platinum oxide and 36 mL of glacial acetic acid were combined in a bottle and shaken (Parr apparatus) under an atmosphere of hydrogen (40 psi) for 1.5 hours. The mixture was diluted with ethanol and filtered through a pad of diatomaceous earth (Celite (trademark)), and the filtrate was concentrated in vacuo. The residue was made basic cautiously using saturated aqueous NaHCO_3 , diluted with H_2O and extracted with two portions of CH_2Cl_2 . The organic fractions were dried (Na_2SO_4) and concentrated with a rotary evaporator to obtain 1.4 g of oil. This material was subjected to flash column chromatography using 8:1 hexanes/ethyl acetate as the eluant to obtain 800 mg of the title compound as a solid, m.p. 70-73°C.

^1H NMR (CDCl_3) δ 1.02 (t, 3H, $J=8$), 1.15-1.80 (m, 8H), 1.88-1.98 (m, 1H), 2.15-2.28 (m, 3H), 2.85-2.92 (m, 1H), 3.08 (bs, 1H), 3.82-4.05 (m, 3H), 7.10-7.18 (m, 1H), 7.25-7.42 (m, 4H).

C. 2-Carbobenzyloxy-4-carboethoxy-3-phenyl-2-azabicyclo[4.4.0]decane

In a round-bottom flask were placed 900 mg (3.1 mmol) of the title compound from part B above and 7 mL of 10% aqueous NaHCO_3 . To this stirring mixture at 0°C was added 0.49 mL (3.4 mmol) of benzyl chloroformate, and the mixture was stirred at 0°C for 1 hour. The mixture was extracted

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with two portions of ethyl ether, and the ethyl ether fractions were washed with brine, dried (Na_2SO_4) and concentrated with a rotary evaporator to obtain 1.1 g of oil. This material was purified by flash column chromatography to obtain 950 mg of the title compound.

^1H NMR (CDCl_3) δ 0.80-1.75 (m, 11H), 1.88-2.00 (m, 2H), 2.37-2.45 (m, 1H), 2.90-3.00 (m, 1H), 3.98-4.43 (m, 3H), 5.18-5.38 (m, 2H), 6.00 - 6.15 (2d, 1H, $J=6$), 7.13-7.55 (m, 10H).

10 D. 2-Carbobenzyloxy-4-carboxamido-3-phenyl-2-azabicyclo[4.4.0]decane

Under a nitrogen atmosphere in a round-bottom flask were placed 572 mg (10.7 mmol) of ammonium chloride and 8 mL of benzene. To this system was added 5.4 mL of 2M trimethylaluminum in hexanes. To this stirring mixture at 0°C was added 900 mg (2.30 mmol) of the title compound from part C above in 12 mL of benzene, and the reaction mixture was heated at 50°C overnight. The system was cooled in an ice bath, the reaction was slowly quenched with 8 mL of 1M aqueous HCl, and the mixture was stirred for 0.5 hours. The mixture was filtered through diatomaceous earth (Celite (trademark)) and the filter pad was washed with saturated aqueous NaHCO_3 and CH_2Cl_2 . The layers were separated, the aqueous phase was extracted with CHCl_3 and the combined organic fractions were dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified by flash column chromatography using 1:49 methanol/ CHCl_3 as the eluant to obtain 450 mg of the title compound.

^1H NMR (CDCl_3) δ 0.72-2.00 (m, 10H), 2.28-2.45 (m, 1H), 2.82-2.90 (m, 1H), 4.18-4.43 (m, 1H), 5.15-5.85 (m, 4H), 5.88 - 5.98 (2d, 1H, $J=6$), 7.18-7.52 (m, 10H).

E. 4-Amino-2-carbobenzyloxy-3-phenyl-2-azabicyclo[4.4.0]decane

In a round-bottom flask were placed 400 mg (1.02 mmol) of the title compound from part D above and 2 mL of CH_3CN . To the system were added 2 mL of H_2O and 639 mg (1.48 mmol) of bis-(trifluoroacetoxy)iodobenzene. The reaction mixture was

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stirred at room temperature overnight. The reaction mixture was partitioned between ether and 1M aqueous HCl, the layers were separated and the ether phase was extracted with 1M aqueous HCl. The combined aqueous fractions were

5 neutralized with saturated aqueous NaHCO₃ and extracted with two portions of ether. These combined ether extracts were washed with brine, dried (Na₂SO₄) and concentrated with a rotary evaporator to obtain 200 mg of the title compound.

¹H NMR (CDCl₃) δ 1.00-1.72 (m, 11H), 2.02-2.15 (m, 1H),
10 2.22-2.45 (m, 1H), 3.28-3.40 (m, 1H), 4.10-4.35 (m, 1H),
5.21 (d, 2H, J=6), 5.35-5.66 (m, 1H), 7.15-7.80 (m, 10H).

F. 2-Carbobenzyloxy-4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo[4.4.0]decane

Under a nitrogen atmosphere in a round-bottom flask
15 were placed 200 mg (0.55 mmol) of the title compound from part E above and 2 mL of methanol. To the system was added ca. 0.5 g of 3Å molecular sieves, and the pH of the mixture was adjusted to ca. 4 using methanol saturated with HCl. To the system was added 38 mg (0.60 mmol) of sodium
20 cyanoborohydride in portions, and the pH of the system was adjusted to ca. 4 as above. To the system was added 89 mg (0.66 mmol) of o-anisaldehyde, and the reaction mixture was stirred at room temperature overnight.

The reaction mixture was made basic using saturated
25 aqueous sodium bicarbonate and filtered through a pad of diatomaceous earth (Celite(trademark)). The pad was rinsed with methanol and CH₂Cl₂. The filtrate was concentrated in vacuo, and the residue was partitioned between CH₂Cl₂ and H₂O. The layers were separated, the aqueous phase was extracted
30 with CH₂Cl₂ and the combined organic fractions were dried (Na₂SO₄) and concentrated with a rotary evaporator to obtain 220 mg of oil. The crude material was purified by flash column chromatography to obtain 110 mg of the title compound.

35 ¹H NMR (CDCl₃) δ 0.98-2.04 (m, 11H), 2.20-2.38 (m, 1H),
2.98-3.16 (m, 1H), 3.66 (s, 3H), 3.77 (s, 2H), 4.10-4.32 (m,

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1H), 5.10-5.24 (m, 2H), 5.54-5.74 (2bs, 1H), 6.70-6.88 (m, 2H), 7.00-7.40 (m, 10H), 7.66-7.84 (m, 2H).

G. 4-(2-Methoxybenzyl)amino-3-phenyl-2-azabicyclo-[4.4.0]decane hydrochloride

- 5 Under a nitrogen atmosphere in a round-bottom flask were placed 110 mg (0.23 mmol) of the title compound from part F above and 1.5 mL of ethanol. To the system were added 72 mg (1.2 mmol) of ammonium formate and 110 mg of 10% Pd/C, and the mixture was stirred at room
- 10 temperature for 3 hours. The reaction mixture was filtered through a pad of diatomaceous earth, and the pad was rinsed with ethanol and CH₂Cl₂. The filtrate was concentrated, and the residue was partitioned between CH₂Cl₂ and saturated aqueous NaHCO₃. The layers were separated and the aqueous
- 15 phase was extracted with CH₂Cl₂. The combined organic fractions were dried (Na₂SO₄) and concentrated to obtain 75 mg of oil. This material was dissolved in CH₂Cl₂, and the solution was extracted with two portions of 1M aqueous HCl. The combined aqueous extracts were washed with CH₂Cl₂ and
- 20 made basic with 1M aqueous NaOH. The aqueous fraction was extracted with two portions of CH₂Cl₂, and these combined extracts were dried (Na₂SO₄) and concentrated with a rotary evaporator to obtain 63 mg of oil. This material was diluted with CH₂Cl₂, and ether saturated with HCl was added
- 25 to the system. Concentration and trituration with ether afforded 60 mg of the title compound as its HCl salt, mp 195-198°C.

- ¹H NMR (CDCl₃) δ 1.42-2.04 (m, 12H), 2.34-2.48 (m, 1H), 2.72-2.80 (m, 1H), 2.98-3.04 (m, 1H), 3.38 (d, 1H, J=12),
- 30 3.42 (s, 3H), 3.58 (d, 1H, J=12), 3.95 (d, 1H, J=3), 6.66 (d, 1H, J=8), 6.80 (t, 1H, J=6), 6.97 (d, 1H, J=8), 7.10-7.30 (m, 6H).

EXAMPLE 3

- 3-(2-Methoxybenzyl)amino-2-phenyl-1,2,3,4-
- 35 tetrahydro-quinoline

In a bottle were placed 800 mg (2.9 mmol) of 3-carboethoxy-2-phenylquinoline, 0.174 mL (3.0 mmol) of

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acetic acid, 80 mg of PtO_2 and 48 mL of ethanol, and the mixture was shaken under an atmosphere (40 psi) of hydrogen (Parr apparatus) for 6 hours at room temperature. The mixture was filtered through diatomaceous earth
5 (Celite(trademark)), and the filter pad was rinsed with ethanol. The filtrate was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and saturated aqueous sodium bicarbonate, the layers were separated, the aqueous phase was extracted with CH_2Cl_2 and the combined organic
10 fractions were dried (Na_2SO_4) and concentrated. The crude material was purified by flash column chromatography to obtain 260 mg of 3-carboethoxy-2-phenyl-1,2,3,4-tetrahydroquinoline.

^1H NMR (CDCl_3) δ 1.20 (t, 3H, J=6), 2.85-2.95 (m, 2H),
15 3.22-3.30 (m, 1H), 4.08-4.18 (m, 2H), 4.42 (bs, 1H), 4.95 (d, 1H, J=4), 6.60 (d, 1H, J=10), 6.70 (t, 1H, J=8), 7.02-7.34 (m, 7H).

This material was converted to the title compound using procedures analogous to those of Examples 2B-2G.

20 ^1H NMR (CDCl_3) δ 2.62-2.74 (m, 1H), 2.84-2.94 (m, 1H), 3.12-3.21 (m, 1H), 3.59 (s, 3H), 3.74 (d, 1H, J=9), 3.82 (d, 1H, J=9), 4.61 (d, 1H, J=3), 6.50-6.82 (m, 4H), 6.92-7.36 (m, 9H).

EXAMPLE 4

25 Trans-4-(2-methoxybenzylamino)-2-methyl-3-phenyl-3,4-dihydro-1(2H)-isoquinolinone

A solution of trans-4-amino-2-methyl-3-phenyl-3,4-dihydro-1(2H)-isoquinolinone (2.36 g, 9.36 mmol), prepared according to the method of I. Attanassova et al., Commun. Dept. Chem., Bulg. Acad. Sci., 17(2), 172-9 (1984), in 40
30 mL acetic acid was treated with 1.5 g of 3Å molecular sieves (Aldrich Chemical Co.) followed by the addition of 1.59 g (11.7 mol) of ortho-anisaldehyde. Sodium triacetoxymethylborohydride (Aldrich) was added in three 1.32 g
35 portions (total of 3.97 g, 18.7 mmol), and then stirred at 25 °C overnight. The sieves were removed by filtration through a pad of diatomaceous earth (Celite (trademark)),

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the pad being washed with additional acetic acid, and the combined filtrates were concentrated in vacuo. The residue was treated with 30 mL H₂O, acidified with 1 N HCl and extracted with diethyl ether. The aqueous layer was made
5 alkaline with 2 N NaOH and was reextracted with diethyl ether. After drying over MgSO₄, the ether was removed in vacuo to give the crude title compound as an oil (1.65 g). Chromatography on silica gel (230-400 mesh) eluting with methylene chloride:methanol:concentrated ammonium hydroxide
10 (97:2:1) gave the pure trans isomer of the title compound as a clear oil (0.80g, 23%).

MS, m/e 372 (M+), 253, 132, 121.

¹H NMR (300 MHz, CDCl₃, δ) 3.14 (s, 3H), 3.78 (s, 3H), 3.72-3.92 (m, 3H), 4.88 (bs, 1H), 6.82-6.98 (m, 4H), 7.10-
15 7.42 (m, 9H), 8.18 (d, 1H).

EXAMPLE 5

Trans-4-(2-methoxybenzylamino)-3-phenyl-3,4-dihydro-1(2H)-isoquinolinone

Using the procedure described in Example 4, trans-4-amino-3-phenyl-3,4-dihydro-1(2H)-isoquinolinone (which
20 was prepared by the method of I. Attanassova *et al.*, Commun. Dept. Chem., Bulg. Acad. Sci., 17 (2), 179-9 (1984) except that N-(trimethylsilyl)benzylidenamine was substituted for N-benzylidenemethylamine in the first step
25 of the synthesis), was immediately reacted with ortho-anisaldehyde to produce the title compound as a pale yellow viscous oil (0.100 g).

MS, m/e 358 (M+), 253, 132, 121.

¹H NMR (CDCl₃, 300 MHz, δ) 3.74 (s, 3H), 3.78-4.00 (m, 3H), 4.94 (t, 1H), 6.16 (bs, 1H), 6.82 (d, 1H), 6.92 (t, 1H), 7.12-7.50 (m, 10H), 8.15 (d, 1H).
30

EXAMPLE 6

Trans-4-(2-methoxybenzylamino)-2-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline

35 The title compound from Example 4 (0.8 g, 2.15 mmol) was dissolved in 10 mL dry THF under nitrogen and treated with lithium aluminum hydride (LAH, 0.4 g, 10.5 mmol).

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After 3 hours the excess LAH was quenched with water and extracted with ethyl acetate. The organic extracts were dried (MgSO_4) and concentrated to an oil (0.60 g).

Chromatography on silica gel (230-400 mesh) eluting with
5 ethyl acetate:hexane (1:1) gave the title compound (R_f 0.17) as a viscous oil.

MS, m/e 359 (M^+), 358 (M^+), 239, 222, 121.

^1H NMR (CDCl_3 , 300 MHz, δ) 2.23 (s, 3H), 3.50-3.99 (m, 9H) 4.12 (d, 1H), 6.74-6.96 (m, 4H), 7.02-7.70 (m, 9H).

10

EXAMPLE 7

Trans-4-(2-methoxybenzylamino)-3-phenyl-1,2,3,4-tetrahydroisoquinoline dihydrochloride

Using the procedure described in Example 6, the title compound from Example 5 (0.25 g, 0.7 mmol) was reduced with
15 0.13 g LAH in 10 mL THF to give, after chromatography on silica gel (230-400 mesh) eluting with methylene chloride:methanol:concentrated ammonium hydroxide (95:4:1), a light brown oil. The oil was treated with gaseous hydrochloric acid in diethyl ether to provide pure trans-4-
20 (2-methoxybenzylamino)-3-phenyl-1,2,3,4-tetrahydroisoquinoline dihydrochloride, mp 138-144 °C.
Anal. for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O} \cdot 2\text{HCl} \cdot \text{H}_2\text{O}$: C 63.45, H 6.48, N 6.43. Found C 63.09, H 6.59, N 6.27.

^1H NMR (free base, CDCl_3 , 300 MHz, δ) 3.54-4.18 (m, 9H),
25 6.78-6.86 (m, 2H), 7.0 (m, 1H), 7.09-7.44 (m, 10H).

EXAMPLE 8

5-(2-Methoxybenzyl)amino-4-benzhydryl-3-azabicyclo-[4.1.0]heptanes

A. 5-Hydroxy-4-benzhydryl-3-azabicyclo[4.1.0]-heptanes
30 To a stirred solution of 2,2-diphenyl-nitroethane (4.21 g, 18.5 mmole) and methyl cis-2-(formyl)cyclopropanecarboxylate (2.61 g, 20.4 mmol) in methylene chloride (50mL) was added basic alumina (20.0 g). The reaction mixture was then stirred at 25°C for 24 hours.
35 At the end of this period, it was filtered, and the alumina was washed with 50% ethyl acetate in hexane. The combined organic solvents were concentrated to afford yellow a oil

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(3.49 g) as a mixture of isomers which was used without purification. This was dissolved in ethanol (65 ml) at 25°C, and to it neutral Raney nickel was added (3.5 g). The reaction mixture was shaken on a Parr shaker under hydrogen
5 (45 psi) for 4 hours; thereafter the reaction mixture was filtered through diatomaceous earth (Celite (trademark)) which was washed thoroughly with ethanol (100 ml), and methylene chloride (100 ml). The organic phases were combined and concentrated under vacuum to a yellow oil (2.65
10 g) which was loaded onto a silica gel column. Elution with 95:5:0.5 methylene chloride:methanol:aqueous ammonia afforded 5-hydroxy-4-benzhydryl-3-azabicyclo[4.1.0]heptanes (0.291 g, mp 250°C, 6%).

IR (film) V_{\max} 3500, 1630, 1650 cm^{-1}

15 ^1H NMR (CDCl_3) δ 1.12-1.3 (2H, m), 1.7-1.8 (2H, m), 3.8 (1H, dd, $J = 1.5, 12$ Hz), 3.87 (1H, bs), 4.22 (1H, d, $J = 11$ Hz), 5.07 (1H, bs), 7.14-7.4 (10H, m).

B. 5-Oxo-4-benzhydryl-3-azabicyclo[4.1.0]heptanes

To a solution of oxalyl chloride (140 mgs, 1.15 mmole)
20 in methylene chloride (3 ml) at -50°C was added dimethyl sulfoxide (180 mgs, 2.3 mmole). To it a solution of 5-hydroxy-4-benzhydryl-3-azabicyclo[4.1.0]heptane (287 mgs, 1.04 mmole) in methylene chloride (4ml) was added and the reaction mixture was further stirred for 15 minutes
25 at 50°C and for 5 minutes at 0°C. Thereafter, triethylamine (0.7 ml) was added, and the reaction mixture was stirred at 25°C for 3 hours. At the end of this period, the reaction mixture was taken up in ether; the organic layer was washed with water and dried (anhyd.
30 MgSO_4). The organic phases were removed under vacuum to afford 5-oxo-4-benzhydryl-3-azabicyclo[4.1.0]heptanes (275 mgs).

^1H NMR (CDCl_3) δ 0.45 (0.6H, q, $J = 5$ Hz), 1.05-1.3 (1.4H, m), 2.0-2.3 (1.4H, m), 2.65-2.85 (0.6H, m), 4.55
35 (0.4H, d, $J = 6$ Hz), 4.7 (0.6H, d, $J = 6$ Hz), 4.75 (0.4H, d, $J = 6$ Hz), 4.82 (0.6H, bd), 5.4 (0.4H, bs), 5.55 (0.6H, bs), 7.1-7.4 (10H, m).

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C. 5-(2-Methoxybenzyl)amino-4-benzhydryl-3-azabicyclo[4.1.0]heptanes

A solution of 5-oxo-4-benzhydryl-3-azabicyclo[4.1.0]heptanes (275 mgs), hydroxyl amine hydrochloride (210 mgs, 3 mmole) and sodium acetate (410 mgs, 5 mmole) in ethanol (15 ml) containing water (2 ml) was stirred at 25°C for 18 hours. At the end of this period, the reaction mixture was concentrated under vacuo and was suspended in water. This, after extractive work up with methylene chloride, afforded 5-oxamino-4-benzhydryl-3-azabicyclo[4.1.0]heptanes (275 mgs). This was used in the next without purification. Thus, to a stirred solution of 5-oxamino-4-benzhydryl-3-azabicyclo[4.1.0]heptanes (275 mgs) in ethanol (10 ml) was added neutral Raney Ni (~0.5 gms) and the Parr bottle was shaken under hydrogen (40 psi). After 4 hours, the reaction mixture was filtered through diatomaceous earth (Celite (trademark)) which was thoroughly washed with ethanol. The organic solvents were removed under vacuum to afford 5-amino-4-benzhydryl-3-azabicyclo[4.1.0]heptane which was converted to the title compound by a procedure similar to that described in Examples 1H and 7.

¹H NMR (CDCl₃) δ 0.3-0.8 (2H, m), 1.0-1.4 (2H, m), 2.6-3.5 (4H, m), 3.7, 3.9 (3H, s), 4.20 (0.4H, d, J = 11 Hz), 4.39, (0.6H, d, J = 11 Hz), 6.7-7.5 (10H, m). HRMS Calculated for C₂₇H₃₀N₂O: 398.2353. Found: 398.2333.

The title compounds of Examples 9 through 14 were prepared by a procedure similar to that described in Example 1.

30

EXAMPLE 9

[1α,3α,4β,5α]-4-(2-chlorobenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane

¹H NMR (CDCl₃) δ 1.4-2.1 (6H, m), 2.73 (1H, quin, J = 7.5 Hz), 3.12 (1H, dd, J = 7.5, 9.5 Hz), 3.55 (1H, dd, J = 13 Hz), 3.72 (1H, dd, J = 13 Hz), 3.8 (1H, d, J = 13.5 Hz), 3.93 (1H, m), 7.0-7.4 (9H, m).

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^{13}C -NMR (CDCl_3) δ 25.7, 26.4, 37.4, 45.5, 52.6, 62.3, 66.0, 68.1, 126.8, 127.4, 127.5, 128, 128.3, 128.5, 140.5, 142.0.

HRMS Calculated for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{Cl}$: 326.1544. Found:

5 326.1481.

EXAMPLE 10

[1 α ,3 α ,4 β ,5 α]-4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane

^1H NMR (CDCl_3 , δ 1.4-2.1 (6H, m), 2.69 (1H, quin, $J=7.5$ Hz), 2.96 (1H, dd, $J=7.5$, 9.5 Hz), 3.53 (3H, s), 3.56 (1H, dd, $J=13.5$ Hz), 3.74 (1H, dd, $J=13.5$ Hz), 3.56 (1H, d, $J=9.5$ Hz), 3.86-3.92 (1H, m), 6.74 (1H, d, $J=8.2$ Hz), 6.83 (1H, dt, $J=7.0$, 1.0 Hz), 7.05 (1H, dd, $J=7.5$, 2.0 Hz), 7.1-7.4 (6H, m).

15 HRMS Calc'd for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}$: 322.2045.

Found: 322.2056.

Anal. calc'd for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O} \cdot 2\text{HCl} \cdot 1/4\text{H}_2\text{O}$: C, 63.08; H, 7.18; N, 7.01 Found: C, 62.89; H, 6.96; N, 7.01.

EXAMPLE 11

20 [1 α ,3 α ,4 α ,5 α]-4-(2,5-Dimethoxybenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane

^1H NMR (CDCl_3) δ 1.2-1.45 (2H, m), 1.5-1.8 (1H, m), 1.8-2.0 (3H, m), 2.59 (1H, dd, $J=15.4$, 7 Hz), 2.92 (1H, dd, $J=4.5$, 1.5 Hz), 3.49 (3H, s), 3.48 (1H, d, $J=13.5$ Hz), 3.71 (1H, d, $J=13.5$ Hz), 3.72 (3H, s), 3.95-4.05 (1H, m), 4.28 (1H, d, $J=4.5$ Hz), 6.6-6.75 (3H, m), 7.2-7.4 (5H, m).

^{13}C NMR (CDCl_3) δ 25.9, 31.5, 35.2, 47.2, 48.6, 55.3, 55.7, 62.5, 64.3, 67.5, 110.7, 112.2, 116.1, 126.8, 127.2, 128.3, 129.1, 139.1, 151.9, 153.2.

30

EXAMPLE 12

[1 α ,3 α ,4 α ,5 α]-4-(2-Methoxy-5-chlorobenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane

^1H NMR (CDCl_3) δ 1.25-1.55 (3H, m), 1.6-1.7 (1H, m), 1.8-2.05 (2H, m), 2.63 (1H, dd, $J=17$, 8.5 Hz), 2.91 (1H, dd, $J=4.6$, 1.5 Hz), 3.51 (3H, s), 3.54 (1H, d, $J=13.5$ Hz), 3.78 (1H, d, $J=13.5$ Hz), 3.95-4.05 (1H, m), 4.28 (1H, d,

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J=4.5 Hz), 6.74 (1H, d, J=8.2 Hz), 6.84 (1H, dt, J=7.4, 1Hz), 7.03 (1H, dd, J=7.3, 1.7 Hz), 7.15-7.4 (5H, m).

¹³C NMR (CDCl₃) δ 25.9, 31.5, 35.1, 47.2, 48.4, 54.8, 62.6, 64.2, 67.4, 109.9, 120.2, 126.8, 127.2, 127.5, 128.3, 5 128.4, 130.1, 138.7, 157.7.

EXAMPLE 13

[1α,3α,4α,5α]-4-(2-Methoxy-5-methylbenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane

¹H NMR (CDCl₃) δ 1.25-1.45 (3H, m), 1.6-1.75 (1H, m), 10 1.85-2.05 (2H, m), 2.23 (3H, s), 2.61 (1H, dd, J=16.8, 8.6 Hz), 2.91 (1H, dd, J=5, 1.5 Hz), 3.49 (3H, s), 3.49 (1H, d, J=13.5 Hz), 3.7 (1H, d, J=13.5 Hz), 3.95-4.05 (1H, m), 4.27 (1H, d, J=4.5 Hz), 6.62 (1H, d, J=8.3 Hz), 6.82 (1H, d, J=2 Hz), 6.9 (1H, dd, J=8.2, 1.8 Hz), 7.15-7.35 (5H, m).

15 ¹³C NMR (CDCl₃) δ 20.4, 25.9, 31.5, 35.2, 47.2, 48.6, 54.9, 62.5, 64.3, 67.6, 109.9, 126.7, 127.2, 127.7, 128.2, 128.3, 130.7, 139.1, 155.6.

HRMS Calc'd for C₂₂H₂₈N₂O: 336.4760. Found: 336.2200.

EXAMPLE 14

20 [1α,3α,4α,5α]-4-(2,5-Methoxy-5-fluorobenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane

¹H NMR (CDCl₃) δ 1.3-1.5 (3H, m), 1.6-1.75 (1H, m), 1.8-2.0 (2H, m), 2.6 (1H, dd, J=17, 8.5 Hz), 2.91 (1H, dd, J=4.6, 1.7 Hz), 3.48 (1H, d, J=14 Hz), 3.51 (3H, s), 3.69 25 (1H, d, J=14 Hz), 3.9-4.1 (1H, m), 4.31 (1H, d, J=4.5 Hz), 6.64 (1H, dd, J=9, 4.3 Hz), 6.77 (1H, dd, J=8.8, 3.1 Hz), 6.85 (1H, dd, J=8.6, 3.2 Hz), 7.2-7.5 (5H, m).

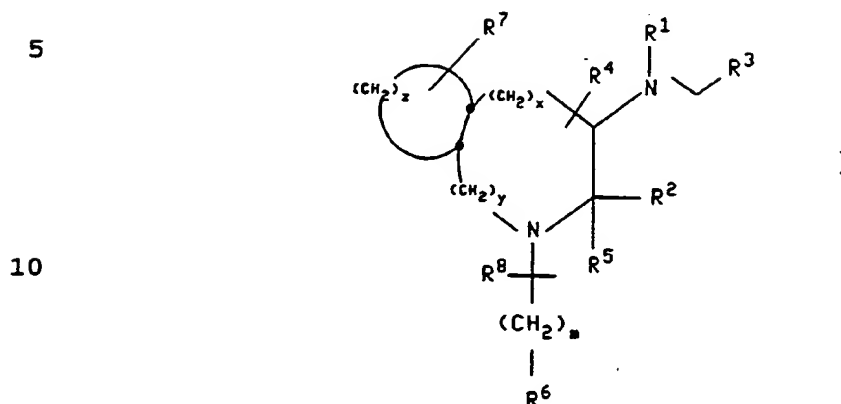
¹³C NMR (CDCl₃) δ 25.9, 31.4, 46.7, 48.6, 55.4, 62.5, 64.3, 67.4, 110.5, 110.6, 113.4, 113.7, 116.4, 116.7, 127, 30 127.2, 128.4, 138.6, 153.6, 158.3.

HRMS Calc'd for C₂₁H₂₅N₂OF: 340.4393. Found: 340.1944.

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CLAIMS

1. A compound of the formula



15 wherein x is an integer from zero to four;

y is an integer from zero to four;

z is an integer from one to six;

the ring containing $(CH_2)_z$ may contain from zero to three double bonds, and one of the carbons of $(CH_2)_z$ may optionally be replaced by oxygen, sulfur or nitrogen;

20

m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double or triple bond and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^8 ;

25

R^1 is hydrogen or (C_1-C_6) alkyl optionally substituted with hydroxy, alkoxy or fluoro;

R^2 is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl groups may optionally be substituted with

30

35

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one or more substituents independently selected from halo, nitro, (C₁-C₆)alkyl, (C₁-C₆) alkoxy, trifluoromethyl, amino,

- 5 (C₁-C₆)-alkylamino, (C₁-C₆)alkyl-O-C(=O)-, (C₁-C₆)alkyl-O-C(=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)-O-, (C₁-C₆)alkyl-C(=O)-(C₁-C₆)alkyl-O-,
- 10 (C₁-C₆)alkyl-C(=O)-, (C₁-C₆)alkyl-C(=O)-(C₁-C₆)alkyl-,
- 15 di-(C₁-C₆) alkylamino, -CNH-(C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)-NH-
- 20 (C₁-C₆)alkyl, -NHCH and -NHC-(C₁-C₆)alkyl;
- R⁵ is hydrogen or (C₁-C₆)alkyl;
- or R² and R⁵, together with the carbon to which
- 25 they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms, wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;
- R³ is aryl selected from phenyl and naphthyl;
- heteroaryl selected from indanyl, thienyl, furyl, pyridyl,
- 30 thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; or cycloalkyl having from three to seven carbon atoms, wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur;
- wherein each of said aryl and heteroaryl groups may
- 35 optionally be substituted with one or more substituents, and said (C₃-C₇) cycloalkyl may optionally be substituted with one or two substituents, said substituents being independently selected from halo, nitro, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, trifluoromethyl, amino, phenyl, (C₁-C₆)-
- 40 alkylamino, -CNH-(C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)-NH-(C₁-C₆)alkyl, -NHCH and -NHC-(C₁-C₆) alkyl;

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R^4 may be attached to any atom of the nitrogen containing ring having an available bonding site and R^7 may be attached to any atom of the $(CH_2)_z$ containing ring having an available bonding site;

- 5 R^4 , R^6 , R^7 and R^8 are each independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxyalkyl, (C_1-C_6) alkylamino, di- (C_1-C_6) alkylamino, (C_1-C_6) alkoxy, $(C_1-$

10 $C_6)$ alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)- (C_1-C_6) alkyl, (C_1-C_6) alkyl-C(=O)-

15 O-, (C_1-C_6) alkyl-C(=O)- (C_1-C_6) alkyl-O- (C_1-C_6) alkyl-C(=O)-, $(C_1-$

$C_6)$ alkyl-C(=O)- (C_1-C_6) alkyl, and the radicals set forth in the

- 20 definition of R^2 , with the proviso that (a) when m is 0, R^8 is absent, (b) neither R^4 , R^6 , R^7 nor R^8 can form, together with the carbon to which it is attached, a ring with R^5 , and (c) R^4 and R^7 can not be attached to the same carbon atom; or a pharmaceutically acceptable salt thereof.

- 25 2. A compound according to claim 1, wherein R^1 , R^4 , R^5 , R^6 , R^7 and R^8 are hydrogen; R^2 is phenyl; R^3 is methoxyphenyl wherein the phenyl moiety is substituted with hydrogen, chlorine, fluorine, (C_1-C_6) alkoxy or trifluoromethane; m is zero; and each of x , y and z is an
30 integer from zero to four.

3. A compound according to claim 1, wherein said compound is $[1\alpha, 3\alpha, 4\alpha, 5\alpha]$ -4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane.

35 4. A compound according to claim 1, wherein said compound is 4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo[4.4.0]decane.

5. A compound according to claim 1, wherein said compound is 4-(2-methoxybenzyl)amino-4-benzhydryl-3-azabicyclo[4.1.0]heptane.

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6. A compound according to claim 1, wherein said compound is [1 α ,3 α ,4 α ,5 α]-4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane.

7. A compound according to claim 1, wherein said
5 compound is 4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo[4.4.0]decane.

8. A compound according to claim 1, wherein said compound is 3-(2-methoxybenzyl)amino-2-phenyl-1,2,3,4-tetrahydroquinoline.

10 9. A compound according to claim 1, wherein said compound is trans-4-(2-methoxybenzylamino)-2-methyl-3-phenyl-3,4-dihydro-1(2H)-isoquinolinone.

10. A compound according to claim 1, wherein said compound is trans-4-(2-methoxybenzylamino)-3-phenyl-3,4-
15 dihydro-1(2H)-isoquinolinone.

11. A compound according to claim 1, wherein said compound is trans-4-(2-methoxybenzylamino)-2-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline.

12. A compound according to claim 1, wherein said
20 compound is trans-4-(2-methoxybenzylamino)-3-phenyl-1,2,3,4-tetrahydroisoquinoline dihydrochloride.

13. A compound according to claim 1, wherein said compound is 5-(2-methoxybenzyl)amino-4-benzhydryl-3-azabicyclo[4.4.1]heptane.

25 14. A compound according to claim 1, wherein said compound is [1 α ,3 α ,4 β ,5 α]-4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane.

15. A compound according to claim 1, wherein said compound is [1 α ,3 α ,4 β ,5 α]-4-(2-chlorobenzyl)amino-3-phenyl-
30 2-azabicyclo[3.3.0]octane.

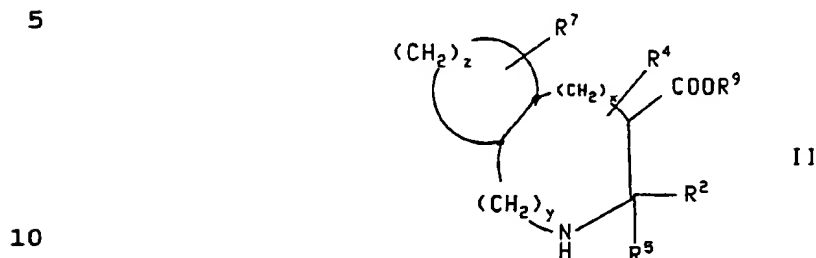
16. A compound according to claim 1, wherein said compound is [1 α ,3 α ,4 α ,5 α]-4-(2,5-dimethoxybenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane.

17. A compound according to claim 1, wherein said
35 compound is [1 α ,3 α ,4 α ,5 α]-4-(2-methoxy-5-chlorobenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane.

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18. A compound according to claim 1, wherein said compound is [1 α ,3 α ,4 α ,5 α]-4-(2-methoxy-5-methylbenzyl)amino-3-phenyl-2-azabicyclo[3.3.0]octane.

19. A compound of the formula



wherein R², R⁴, R⁵, R⁷, x, y and z are defined as in claim 1, and R⁹ is (C₁-C₆)alkyl or hydrogen.

20. A pharmaceutical composition for treating or preventing a condition selected from the group consisting of inflammatory diseases, anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies, chronic obstructive airways disease, hypersensitivity disorders, vasospastic diseases, fibrosing and collagen diseases, reflex sympathetic dystrophy, addiction disorders, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders, disorders related to immune enhancement or suppression and rheumatic diseases in a mammal, comprising an amount of a compound according to claim 1 effective in antagonizing the effect of substance P at its receptor site and a pharmaceutically acceptable carrier.

21. A pharmaceutical composition for treating or preventing a condition selected from the group consisting of inflammatory diseases, anxiety, colitis, depression or dysthymic disorders, psychosis, pain, allergies, chronic obstructive airways disease, hypersensitivity disorders, vasospastic diseases, fibrosing and collagen diseases, reflex sympathetic dystrophy, addiction disorders, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders, disorders related to immune enhancement or suppression and rheumatic diseases in a mammal, comprising an amount of a compound

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according to claim 1 effective in preventing or treating such condition and a pharmaceutically acceptable carrier.

22. A method of treating or preventing a condition selected from the group consisting of inflammatory
5 diseases, anxiety, colitis, depression or dysthymic disorders, psychosis, pain, allergies, chronic obstructive airways disease, hypersensitivity disorders, vasospastic diseases, fibrosing and collagen diseases, reflex
10 sympathetic dystrophy, addiction disorders, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders, disorders related to immune enhancement or suppression and rheumatic diseases in a mammal, comprising administering to a mammal in need of such treatment or prevention an amount of a compound
15 according to claim 1 effective in antagonizing the effect of substance P at its receptor site and a pharmaceutically acceptable carrier.

23. A method of treating or preventing a condition selected from the group consisting of inflammatory diseases
20 anxiety, colitis, depression or dysthymic disorders, psychosis, pain, allergies, chronic obstructive airways disease, hypersensitivity disorders, vasospastic diseases, fibrosing and collagen diseases, reflex sympathetic dystrophy, addiction disorders, stress related somatic
25 disorders, peripheral neuropathy, neuralgia, neuropathological disorders, disorders related to immune enhancement or suppression and rheumatic diseases in a mammal, comprising administering to a mammal in need of such treatment or prevention an amount of a compound
30 according to claim 1 effective in preventing or treating such condition and a pharmaceutically acceptable carrier.

24. A pharmaceutical composition for antagonizing the effect of substance P at its receptor site in a mammal, comprising a substance P antagonizing effective amount of a
35 compound according to claim 1 and a pharmaceutically acceptable carrier.

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25. A method of antagonizing the effect of substance P at its receptor site in a mammal, comprising administering to said mammal a substance P antagonizing effective amount of a compound according to claim 1.

5 26. A pharmaceutical composition for treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound according to claim 1
10 effective in antagonizing the effect of substance P at its receptor site and a pharmaceutically acceptable carrier.

27. A method of treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated
15 neurotransmission, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site in a mammal.

20 28. A pharmaceutical composition for treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound according to claim 1, or
25 a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition and a pharmaceutically acceptable carrier.

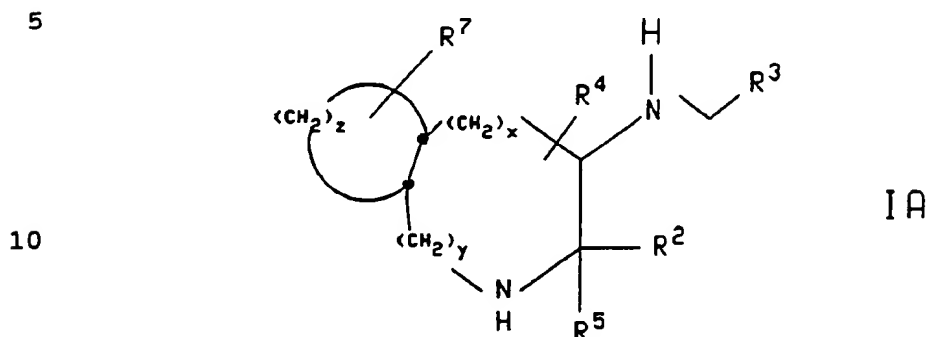
29. A method of treating or preventing a condition in mammal, the treatment or prevention of which is effected or
30 facilitated by a decrease in substance P mediated neurotransmission, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1 effective in treating or preventing such condition.

35 30. A radioactive isotope of a compound according to claim 1.

-61-

31. A compound according to claim 30, wherein said radioactive isotope is a tritium or carbon-14 isotope of a compound according to claim 1.

32. A process for preparing a compound of the formula



wherein x is an integer from zero to four;

y is an integer from zero to four;

15 z is an integer from one to six;

the ring containing $(CH_2)_z$ may contain from zero to three double bonds, and one of the carbons of $(CH_2)_z$ may optionally be replaced by oxygen, sulfur or nitrogen;

20 m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double or triple bond and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^8 ;

25 R^2 is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, 30 tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl groups may optionally be substituted with one or more substituents independently selected from halo, 35 nitro, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, amino,

$$\begin{array}{c} \text{O} \\ || \\ (C_1-C_6)\text{-alkylamino, } (C_1-C_6)\text{alkyl-O-C-} \end{array} \quad \begin{array}{c} \text{O} \\ || \\ (C_1-C_6)\text{alkyl-O-C-(C}_1\text{-} \end{array}$$

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- $$\text{C}_6\text{)alkyl, (C}_1\text{-C}_6\text{)alkyl-C(=O)-, (C}_1\text{-C}_6\text{)alkyl-C(=O)-(C}_1\text{-C}_6\text{)alkyl-O-,}$$
- 5
$$\text{(C}_1\text{-C}_6\text{)alkyl-C(=O)-, (C}_1\text{-C}_6\text{)alkyl-C(=O)-(C}_1\text{-C}_6\text{)alkyl-,}$$
- 10
$$\text{di-(C}_1\text{-C}_6\text{) alkylamino, -CNH(=O)-(C}_1\text{-C}_6\text{)alkyl, (C}_1\text{-C}_6\text{)alkyl-C(=O)-NH-}$$
- 15
$$\text{(C}_1\text{-C}_6\text{)alkyl, -NHCH(=O) and -NHC(=O)-(C}_1\text{-C}_6\text{)alkyl;}$$
- R^5 is hydrogen or (C_1-C_6) alkyl;
 or R^2 and R^5 , together with the carbon to which they
 are attached, form a saturated carbocyclic ring having from
 20 3 to 7 carbon atoms, wherein one of said carbon atoms may
 optionally be replaced by oxygen, nitrogen or sulfur;
 R^3 is aryl selected from phenyl and naphthyl;
 heteroaryl selected from indanyl, thienyl, furyl, pyridyl,
 thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl,
 25 tetrazolyl and quinolyl; or cycloalkyl having from three to
 seven carbon atoms, wherein one of said carbon atoms may
 optionally be replaced by nitrogen, oxygen or sulfur;
 wherein each of said aryl and heteroaryl groups may
 optionally be substituted with one or more substituents,
 30 and said (C_3-C_7) cycloalkyl may optionally be substituted
 with one or two substituents, said substituents being
 independently selected from halo, nitro, (C_1-C_6) alkyl, $(C_1-$
 $C_6)$ alkoxy, trifluoromethyl, amino, phenyl, $(C_1-C_6)-$
 35
$$\text{alkylamino, -CNH(=O)-(C}_1\text{-C}_6\text{)alkyl, (C}_1\text{-C}_6\text{)alkyl-C(=O)-NH-(C}_1\text{-C}_6\text{)alkyl,}$$
- 40
$$\text{-NHCH(=O) and -NHC(=O)-(C}_1\text{-C}_6\text{) alkyl;}$$

R^4 may be attached to any atom of the nitrogen
 containing ring having an available bonding site and R^7 may
 be attached to any atom of the $(CH_2)_2$ containing ring having
 45 an available bonding site;

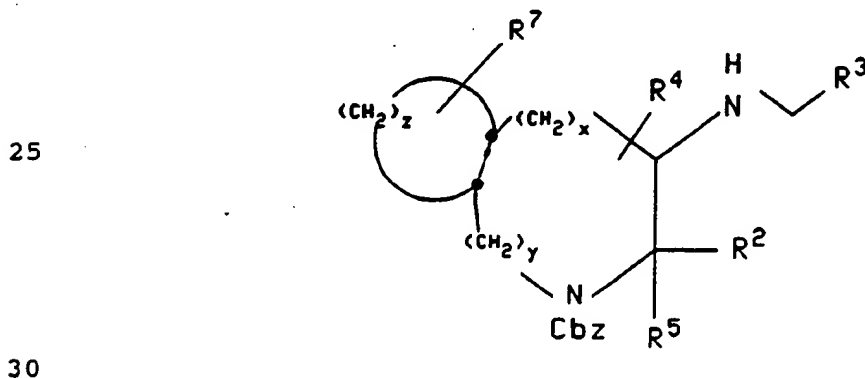
-63-

R^4 , and R^7 are each independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxyalkyl, (C_1-C_6) alkylamino, di- (C_1-C_6) alkylamino, (C_1-C_6) alkoxy, $(C_1-$

5 $C_6)$ alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)- (C_1-C_6) alkyl, (C_1-C_6) alkyl-C(=O)-
10 O-, (C_1-C_6) alkyl-C(=O)- (C_1-C_6) alkyl-O- (C_1-C_6) alkyl-C(=O)-, $(C_1-$

$C_6)$ alkyl-C(=O)- (C_1-C_6) alkyl, and the radicals set forth in the
15 definition of R^2 , with the proviso that (a) neither R^4 nor R^7
can form, together with the carbon to which it is attached,
a ring with R^5 , and (c) R^4 and R^7 can not be attached to the
same carbon atom;

20 or a pharmaceutically acceptable salt thereof,
comprising reacting a compound of the formula



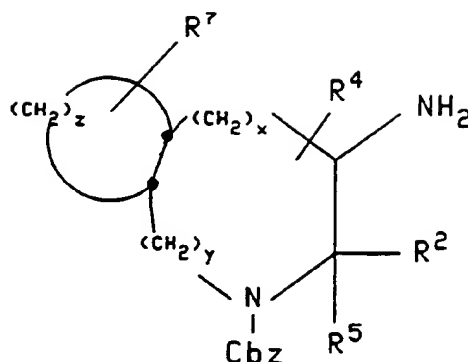
X

wherein R^2 , R^3 , R^4 , R^5 , R^7 , x , y and z are defined as above,
35 with ammonium formate in the presence of palladium on
charcoal.

33. A process according to claim 32, wherein said
compound of formula X is obtained by either:

(a) reductive amination of a compound of the formula
40 R^3CHO , wherein R^3 is defined as in claim 32, in the presence
of a compound of the formula

-64-



IX

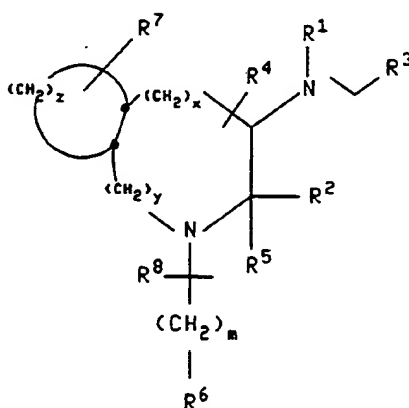
wherein R^2 , R^3 , R^4 , R^5 , R^7 , x , y and z are defined as in claim 32; or

(b) acylating a compound of the formula IX, as defined

O

above, with a compound of the formula R^3CCl , wherein R^3 is defined as in claim 32, and then reducing the resulting amide.

34. A process for preparing a compound of the formula



I

wherein x is an integer from zero to four;
 y is an integer from zero to four;
 z is an integer from one to six;

-65-

the ring containing $(CH_2)_2$ may contain from zero to three double bonds, and one of the carbons of $(CH_2)_2$ may optionally be replaced by oxygen, sulfur or nitrogen;

m is an integer from zero to twelve, and any one of
 5 the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double or triple bond and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^8 ;

R^1 is hydrogen or (C_1-C_6) alkyl optionally substituted
 10 with hydroxy, alkoxy or fluoro;

R^2 is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl;
 15 heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl
 20 and benzhydryl groups may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, amino,

25 (C_1-C_6) -alkylamino, (C_1-C_6) alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)-(C₁-

30 C₆)alkyl, (C_1-C_6) alkyl-C(=O)-O-, (C_1-C_6) alkyl-C(=O)-(C₁-C₆)alkyl-O-,

35 (C_1-C_6) alkyl-C(=O)-, (C_1-C_6) alkyl-C(=O)-(C₁-C₆)alkyl-,

di- (C_1-C_6) alkylamino, -C(=O)NH- (C_1-C_6) alkyl, (C_1-C_6) alkyl-C(=O)-NH-

40 (C_1-C_6) alkyl, -NHCH(=O) and -NHC(=O)- (C_1-C_6) alkyl;

R^5 is hydrogen or (C_1-C_6) alkyl;

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or R² and R⁵, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms, wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;

- 5 R³ is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; or cycloalkyl having from three to seven carbon atoms, wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C₃-C₇) cycloalkyl may optionally be substituted with one or two substituents, said substituents being
- 10 independently selected from halo, nitro, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, trifluoromethyl, phenyl, amino, (C₁-C₆)-

20 alkylamino, $\begin{array}{c} \text{O} \\ || \\ -\text{CNH}-(\text{C}_1-\text{C}_6)\text{alkyl} \end{array}$, $\begin{array}{c} \text{O} \\ || \\ (\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}-\text{NH}-(\text{C}_1-\text{C}_6)\text{alkyl} \end{array}$, $\begin{array}{c} \text{O} \\ || \\ -\text{NHCH} \end{array}$ and $\begin{array}{c} \text{O} \\ || \\ -\text{NHC}-(\text{C}_1-\text{C}_6)\text{alkyl} \end{array}$;

- 25 R⁴ may be attached to any atom of the nitrogen containing ring having an available bonding site and R⁷ may be attached to any atom of the (CH₂)₂ containing ring having an available bonding site;

R⁴, R⁶, R⁷ and R⁸ are each independently selected from

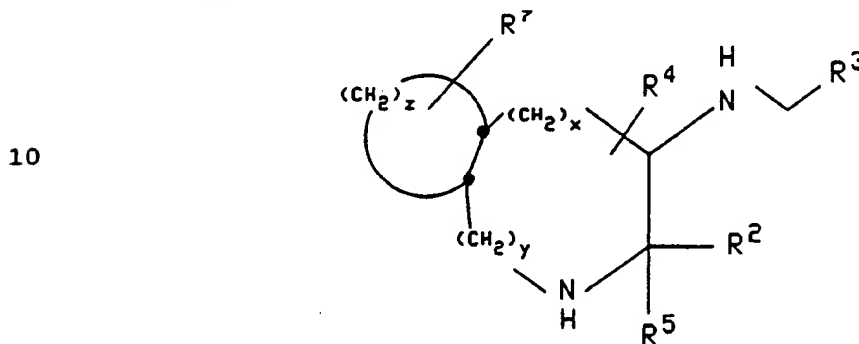
30 hydrogen, hydroxy, halo, amino, carboxy, carboxyalkyl, (C₁-C₆)alkylamino, di-(C₁-C₆)alkylamino, (C₁-C₆)alkoxy, (C₁-

35 C₆)alkyl-O-C-, $\begin{array}{c} \text{O} \\ || \\ (\text{C}_1-\text{C}_6)\text{alkyl}-\text{O}-\text{C}-(\text{C}_1-\text{C}_6)\text{alkyl} \end{array}$, $\begin{array}{c} \text{O} \\ || \\ (\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}- \end{array}$, O-, $\begin{array}{c} \text{O} \\ || \\ (\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}-(\text{C}_1-\text{C}_6)\text{alkyl}-\text{O}-(\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}- \end{array}$, $\begin{array}{c} \text{O} \\ || \\ (\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}-(\text{C}_1-\text{C}_6)\text{alkyl} \end{array}$, and the radicals set forth in the

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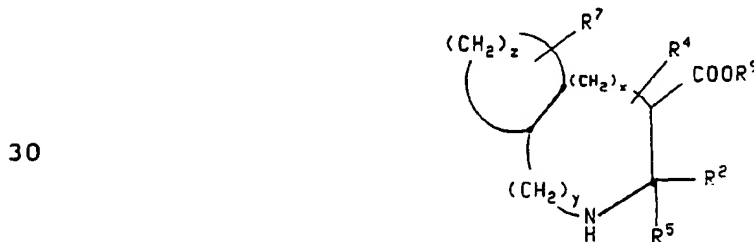
definition of R^2 , with the proviso that (a) when m is 0, R^8 is absent, (b) neither R^4 , R^6 , R^7 nor R^8 can form, together with the carbon to which it is attached, a ring with R^5 , and (c) R^4 and R^7 can not be attached to the same carbon atom;
 5 or a pharmaceutically acceptable salt thereof,
 comprising reacting a compound of the formula



I A

wherein R^2 , R^3 , R^4 , R^5 , R^7 , x , y and z are defined as above,
 20 with a compound of the formula $R^6-(CH_2)_m-X$, wherein m and R^6 is defined as above and X is a leaving group, and wherein one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond and wherein one of the carbons of $(CH_2)_m$ may optionally be
 25 substituted with R^8 , wherein R^8 is defined as above.

35. A process for preparing a compound of the formula



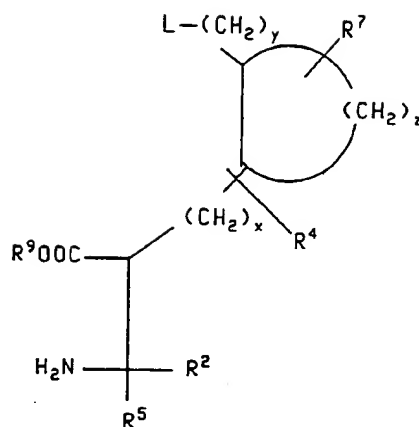
I I

35 wherein R^9 is (C_1-C_4) alkyl and R^2 , R^4 , R^5 , R^7 , x , y and z are defined as in claim 34, comprising heating a compound of the formula

-68-

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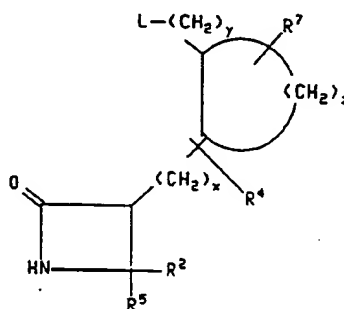
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wherein R^9 is (C_1-C_4) alkyl, L is a leaving group and R^2 , R^4 , R^5 , R^7 , x , y and z are defined as in claim 34.

36. A process according to claim 5, wherein said compound of formula V is obtained by reacting a β -lactam of the formula

20



25

wherein L is a leaving group and R^2 , R^4 , R^5 , R^7 , x , y and z are defined as in claim 34, with an acid.

37. A process according to claim 32 that produces a compound of the formula IA wherein y is zero, z is greater than one and R^5 is hydrogen.

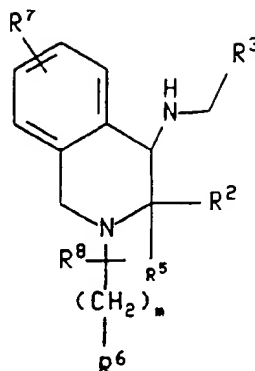
38. A process according to claim 33 that produces a compound of the formula IA, as defined in claim 1, wherein y is zero, z is greater than one and R^5 is hydrogen.

39. A process for preparing a compound of the formula

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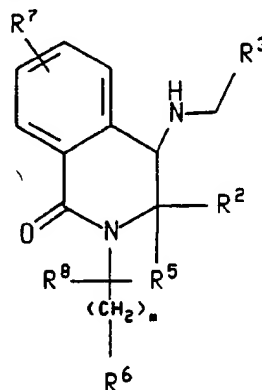


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ID

wherein R^2 , R^3 , R^5 , R^6 , R^7 , R^8 and m are defined as in claim 34, comprising reducing a compound of the formula

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XVIII

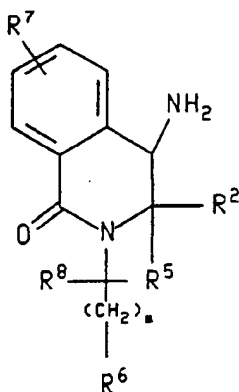
wherein R^2 , R^3 , R^5 , R^6 , R^7 , R^8 and m are defined as in claim 34.

25

40. A process according to claim 39, wherein said compound of the formula XVIII is obtained by either:

(a) reductive amination of a compound of the formula

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XVII

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wherein R^2 , R^5 , R^6 , R^7 , R^8 , and m are defined as in claim 34,
or

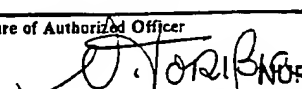
(b) acylating a compound of the formula XVII, as

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defined above, with a compound of the formula $R^3\text{CCl}$, wherein
 R^3 is defined as in claim 34, and then reducing the
resulting amide.

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶			
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl.5 C 07 D 209/52 A 61 K 31/395 C 07 D 215/38 C 07 D 217/22 C 07 D 221/04 // C 07 D 215/54 C 07 D 217/26			
II. FIELDS SEARCHED			
Minimum Documentation Searched ⁷			
Classification System	Classification Symbols		
Int.Cl.5	C 07 D 209/00 C 07 D 215/00 C 07 D 217/00 C 07 D 221/00		
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸			
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹			
Category ^o	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²		Relevant to Claim No. ¹³
X	US,A,3452026 (Y.G. PERRON et al.) 24 June 1969, see column 8, claim 1; column 10, claim 12; column 7, line 47 and lines 49-58; column 5, lines 35-36 ---		1,21
X	FR,A,1555552 (INSTITUT PASTEUR) 31 January 1969, see page 4, examples 14 and 16 ---		19
X	EP,A,0050881 (ELI LILLY AND COMPANY) 5 May 1982, see page 26; claim 1; pages 11-13; example 1 ---		19
X	Chemical Abstracts, volume 86, no. 17, 25 April 1977, (Columbus, Ohio, US) see page 534, column 1, abstract 121189c, & JP, A, 76115484 (GRELAN PHARMACEUTICAL CO., LTD) 12 October 1976 --- -/-		19
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>^o Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>			
IV. CERTIFICATION			
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report	
21-01-1992		04. 03. 92	
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer  D. TORIPIO	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	WO,A,9005729 (PFIZER INC.) 31 May 1990, see the whole document (cited in the application) -----	1,20

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:
 Please see PCT-RULE 39.1(iv)!
 Although claims 22,23,25,27,29 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound /composition.
2. ☐ Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:
3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this International application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims.
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9105776
SA 52563

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